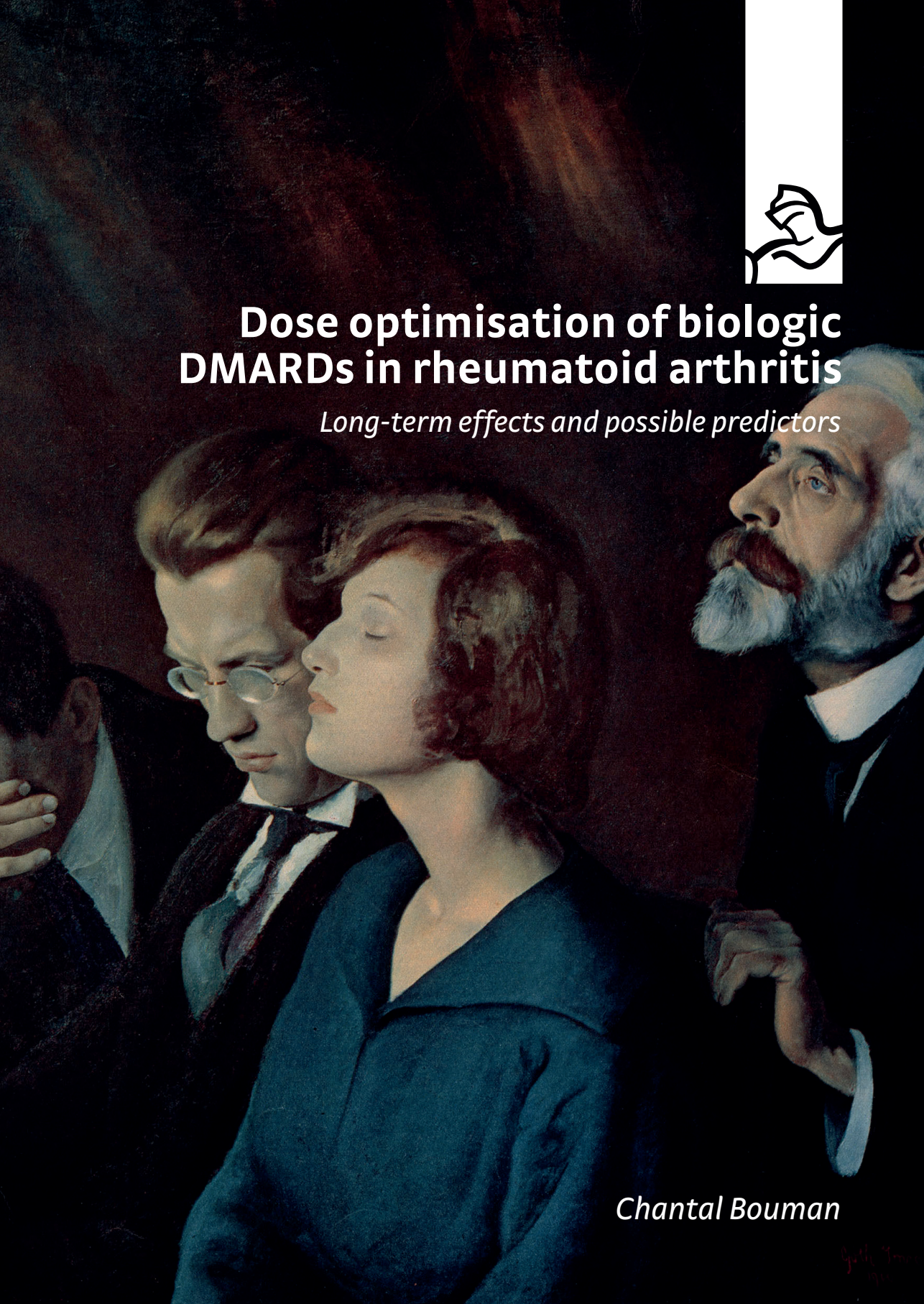

Dose optimisation of biologic DMARDs in rheumatoid arthritis

Long-term effects and possible predictors

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Table of contents

Chapter 1

General introduction

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic autoimmune disease of unknown etiology. In a general adult population, the prevalence is 0.5-1%, with women being affected significantly more often than men (female:male ratio three:one). RA can occur at any age, but first symptoms most frequently emerge between the fourthth and sixth decade.[1,2] Classical symptoms include a symmetrical polyarthritis of small synovial joints of hands and feet, although larger joints may also be involved. Direct symptoms of arthritis include pain, swelling and stiffness. In the long term, ongoing inflammation leads to joint destruction with consequent disability and loss of quality of life.[3-6] Systemic symptoms can also occur, including vasculitis, interstitial lung fibrosis and rheumatoid nodules.[1,2] Furthermore, persistent systemic inflammation is associated with an increased risk of infection, malignancies and cardiovascular disease.[1,7-11] Therefore, the aim of treatment is to inhibit the inflammatory process, thus treating symptoms and preventing both direct and indirect damage.

Pharmacological treatment options

Until the last two decades, the therapeutic arsenal for RA was limited to glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) and conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) (including amongst others azathioprine, methotrexate, hydroxychloroquine, sulfasalazine and leflunomide). Due to recent developments in the understanding of the pathogenesis of RA, a new class of drugs, biologic DMARDs (bDMARDs), has been developed. bDMARDs have specific points of action that include cellular (B- or T-cells) as well as cytokine targets. Among some of the first developed bDMARDs in RA are tumor necrosis factor inhibitors (TNFi), which are named after their property to block the cytokine tumor necrosis factor.[12] TNFi are the most widely used bDMARDs and they include adalimumab, certolizumab, etanercept, golimumab and infliximab. bDMARDswith other modes of action are abatacept (T-cell co-stimulation inhibitor), anakinra (Il-1 inhibitor), rituximab (inhibitor of CD-20 expressing B-cells) and tocilizumab (Il-6 inhibitor). All these bDMARDs have proven to be effective RA treatment options by improving clinical, functional and radiographic outcome measures.[13-17] Another recently introduced class of drugs consists of the targeted synthetic DMARDs (tsDMARDs) that include tofacitinib and bariticinib (both Janus Kinase Inhibitors). Currently, within these two classes, new drugs are still being developed, further expanding the treatment options for RA patients.

Treatment strategies

Concurrent with the development of new treatment options, treatment strategies have also changed fundamentally the last few years. The current treatment goal is first to achieve remission early after onset of RA, and then to maintain the lowest disease activity possible. To achieve low disease activity or remission as soon as possible, treatment should be initiated early in the course of the disease and it should include combinations of multiple anti-rheumatic drugs.[18,19] This concept is known as ‘hit hard, hit early’. Several studies have shown that the use of this strategy prevents radiographic joint damage.[20-24] As soon as low disease activity is reached, the aim is to retain it by tight monitoring of disease activity, setting

treatment targets such as low disease activity or remission, and making treatment alterations accordingly. This is called 'tight control' or 'treat-to-target' and these concepts have shown to improve clinical, functional and radiological outcomes.[25, 26]
Although these developments in treatment options and treatment strategies have improved RA care, the use of bDMARDs comes with some important drawbacks. These include (sometimes dose dependent) adverse events like an increased risk of infections and non-melanotic skin cancer, as well as idiosyncratic adverse reactions like the induction of multiple sclerosis, systemic lupus erythematodes or heart failure.[27-31] Furthermore, bDMARDs need to be either administered intravenously at a day care center or self-administered subcutaneously, both posing a burden for patients. Lastly, bDMARDs are expensive (for TNFi in Europe: 14,000 euro per patient per year).[32, 33] However, with the development of biosimilar DMARDs (bsDMARDs) prices have become lower. bsDMARDs are similar to bDMARDs with regard to mode of action, equally effective and safe, but less costly.[34] To optimise treatment and minimise adverse events and costs, a more tailored treatment approach is required. This has lead to another concept and the focal point of this thesis: disease activity guided dose optimisation. This concept includes: 1) starting a bDMARD when it is necessary to achieve or maintain low disease activity, 2) disease activity guided tapering of the bDMARD to the lowest effective dose when a patient has reached low disease activity, or remission, 3) discontinuing the bDMARD when it is no longer required and 4) restarting or re-escalating the bDMARD in case of a flare.

The DRESS study

In a number of previous studies, tapering of TNFi has shown to be feasible and safe in RA patients who are in remission or have achieved low disease activity.[35, 36] Strategy studies that investigate a specific dose optimisation strategy are, however, more scarce. One such study is the DRESS (Dose REduction Strategies of Subcutaneous TNF inhibitors) study.[37] This is a randomised controlled pragmatic, non-inferiority strategy trial on disease activity guided tapering of TNFi in RA patients with stable low disease activity treated with adalimumab or etanercept.[37,38] Patients were randomised to either tapering or continuation of full dose adalimumab or etanercept. Tapering was done in a stepwise manner until discontinuation or until a flare. In case of a flare, the TNFi was restarted or stepwise re-escalated again until the lowest effective dose. Outpatient visits were scheduled every three months up to eightteen months with extra visits in case of flare symptoms. Results showed that disease activity guided dose tapering was feasible in patients with low disease activity or remission and non-inferior to continuation of full dose TNFi with regard to prolonged flare. However, short-lived flares and minimal radiographic progression were more frequently observed in the dose optimisation group. Although these results are very promising, some questions remain on long-term benefits and risks of this dose optimisation strategy. In **chapter 2.1** long-term effects of disease activity guided dose optimisation of adalimumab and etanercept will be presented, by investigating the three-year follow-up data of the DRESS study. Outcomes include disease activity, functioning, short-lived and major flare, radiographic progression and adverse events. Additionally, in **chapter 2.2**, the three-yearcost-effectiveness analysis of the DRESS study is described. Furthermore, it is unclear what exactly causes the additional radiographic progression in patients that had attempted to taper. It can be hypothesised that this is either a temporary effect of the trial-and-error type of tapering strategy, which causes flares and temporary rises in disease activity. It can also be an ongoing process caused by lower TNFi exposition. Therefore, in **chapter 3** possible causes of the minimal increase in radiographic progression in the taper group over eightteen months will be evaluated.

Non TNFi bDMARDS

Feasibility and safety of disease activity guided tapering strategies are shown by results of the DRESS study as well as the STRASS trial (Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study).[37,39] It can be expected that the same will hold true for other bDMARDs like abatacept or tocilizumab. Abatacept and tocilizumab have been proven to be effective treatment options, either as monotherapy or in combination with a csDMARD.[40-46] Tapering or discontinuation of abatacept or tocilizumab has been less extensively investigated compared to tapering or discontinuation of TNFi, but no large differences in the outcomes have been observed.[36] However, most studies on dose optimisation of abatacept or tocilizumab have focussed on early RA patients or are clinical trials with a strict study protocol and a limited follow-up time.[47-51] Since dose optimisation has recently been integrated in international treatment guidelines for RA18, it is interesting to investigate outcomes after dose optimisation in a daily clinical practice setting, with longstanding RA patients, outside a study protocol and with longer follow-up time. In **chapter 4**, dose optimisation of abatacept and tocilizumab in daily clinical practice will be investigated in SONATA (Study ON Abatacept and Tocilizumab Attenuation), a retrospective, explorative cohort study. The chapter will focus on disease activity, functioning, adverse events and persistence of successful tapering or discontinuation.

Predictors of dose optimisation

Current dose optimisation strategies, as described previously, consist of trial-and-error type stepwise tapering until a flare occurs or until the patient can discontinue the drug. This has two important drawbacks. First, temporary flaring is inevitable in a subset of patients. Although temporary flares do not seem to lower levels of functioning or quality of life,[37] they still cause suffering due to pain and stiffness. Prevention of flares could be possible when we would be able to predict which patient can lower the dose or discontinue the drug and which patient cannot. Second, stepwise tapering takes time and is costly. If we would be able to identify which patients can discontinue their drugs, no tapering phase would be necessary, thus saving time and cost. Unfortunately, no such predictors have been identified yet.[52]
One promising predictor for tapering or discontinuation of TNFi might be the multi-biomarker score, or MBDA score. Biomarkers have the practical advantage that there is no need for face-to-face patient contact, which may especially be advantageous for those countries where travel distances to health care facilities are greater. Furthermore, they have the potential for smaller measurement error than clinical disease activity parameters (although this is often not the case). Other claimed advantages might include lower costs and less time-consuming measurements as compared to full joint counts. The MBDA score combines twelve serum biomarkers in an algorithm that provides a score quantifying disease activity in RA patients on a scale from one to a hundred.[53, 54] It was designed to correlate with the disease activity score based on CRP (DAS28-CRP), although the two can be discordant, which could mean either the detection of subclinical synovitis by the MBDA score or false positivity.[55, 56] In a previous study with early RA patients initiating methotrexate treatment, the MBDA score predicted radiographic progression independently of the DAS28.[57] Therefore, the MBDA score

may provide information on disease activity, complementary to DAS28, either DAS28- CRP or -ESR. It may thus also be an interesting candidate predictor for successful tapering or discontinuation of a bDMARD in RA patients. In **chapter 5.1**, we will therefore investigate the MBDA score as possible predictor for these outcomes.

Other possible predictors are serum TNFi drug level and anti-TNFi antibodies. These are proxies for the treatment, not for disease activity. Clinical scenarios have been proposed in which measurement of TNFi drug levels and anti-TNFi antibodies are suggested to be valuable as possible predictor for successful tapering or discontinuation of TNFi in RA patients with low disease activity or remission.[58-60] These scenarios are based on classic pharmacokinetic rules and the assumption that bDMARDs work when the serum drug level remains above the minimal effective drug concentration during the interval between two administrations.[61] This minimal drug concentration varies between patients, which has led to the assumption that each patient has his/her own dose-response curve[62]. Possible dose response curves are 1) normal dose response curve, 2) dose-response curve shifted to the left, thus a lower dose is necessary to obtain good response, 3) dose-response curve shifted to the right, thus a higher dose is necessary to obtain good response, 4) partial response dose response curve, thus the patient only response partially on the drug, 5) flat dose response curve, thus the patient does not respond to the drug at all.63 Based on these curves, two hypotheses can be postulated for dose optimisation in the context of tapering: 1) a patient with low disease activity and a high serum TNFi level has a higher chance of successful tapering, as the drug level is above the higher boundary of the therapeutic window and a clinical effect might be expected also with a lower level and 2) a patient with low disease activity and no or low serum TNFi level and/or anti TNFi antibodies has a higher chance of successful discontinuation, since the drug level is below the lower boundary of the therapeutic window and a clinical effect of the drug might not be present. Although these hypotheses seem rational, studies that test these hypotheses, using the right design, are scarce.[64, 65] **Chapter 5.2** will address these hypotheses.

Finally, in **chapter 6**, a summary and general discussion of our findings and insights from the abovementioned chapters will be provided. I will also propose clinical recommendations and suggestions for future research.

Aim and outline of this thesis

Based on the above-summarised current knowledge on dose optimisation of bDMARDs several questions remain. This thesis aims to answer the following questions:

1. Does the occurrence of prolonged flare remain comparable between TNFi tapering and full dose continuation strategy groups in the long term?
2. Do dose tapering strategies of TNFi lead to less adverse events and lower costs in the long term?
3. What causes a small increase in radiographic progression in TNFi tapering compared to full dose continuation and is this cause only a temporary effect or should we expect more radiographic progression in the long term in patients in whom tapering was attempted?
4. Is dose optimisation of other bDMARDs, like abatacept or tocilizumab, also feasible, effective and safe in RA patients?
5. Can a multi-biomarker score associated with disease activity predict in which RA patients TNFi tapering or discontinuation will be successful?
6. Can serum TNFi levels and anti-TNFi antibodies predict in which RA patients TNFi tapering or discontinuation will be successful?

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1

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Chapter 2

Long-term outcomes of disease-activity-guided dose reduction of TNF inhibition

Chapter 2.1

Long-term outcomes after disease activity guided dose reduction of TNF inhibition in rheumatoid arthritis: 3 year data of the DRESS study, a randomized controlled pragmatic non-inferiority strategy trial

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Abstract

Objective

TNF inhibitors (TNFi) are effective in rheumatoid arthritis (RA), but disadvantages include adverse events (AEs) and high costs. This can be improved by disease activity guided dose reduction (DR). We aimed to assess long-term outcomes of TNFi DR in RA by using 3 year data from the DRESS study.

Methods

In the intervention phase (month 0-18) of the DRESS study, patients were randomized to DR or usual care (UC). In the extension phase (month 18-36), treatment strategies in both groups converged to continuation of protocolized tight control and allowed dose optimization. Intention-to-treat analyses were done on flare, disease activity (DAS28-CRP), functioning (HAQ-DI), quality of life (EQ5D-5L), medication use, radiographic progression (SvdH), and adverse events (AE).

Results

172/180 patients included in the DRESS study were included in the extension phase. Cumulative incidences of major flare were 10% and 12% (-2%, 95%CI -8 to 15) in DR and UC group in the extension phase, and 17% and 14% (3%, 95%CI -9 to 13) from 0-36 months. Cumulative incidences of short-lived flares were 43% (33 to 52%) and 35% (23 to 49%) in DR and UC group in the extension phase, and 83% (75 to 90%) and 44% (31 to 58%) from 0-36 months. Mean DAS28-CRP, HAQ-DI, EQ5D-5L and SvdH remained stable and not significantly different between groups. TNFi use remained low in the DR group, and decreased in the UC group. Cumulative incidences of AE were not significantly different between groups.

Conclusions

Safety and efficacy of disease activity guided TNFi DR in RA are maintained up to three years, with a large reduction in TNFi use, but no other benefits. Implementation of DR would vastly improve the cost-effective use of TNFi.

Introduction

The treatment of rheumatoid arthritis (RA) has improved in the last two decades, due to, amongst other things, the introduction of the first widely used class of anticytokine drugs: TNF inhibitors (TNFi). These drugs are effective and safe in the treatment of RA, providing benefits for symptoms, functioning, quality of life and inhibition of joint damage.[1,2]
However, TNFi are not without their drawbacks. These include (dose dependent) increased risk of infection,[3] skin cancer,[4] and idiosyncratic adverse reactions like induction of multiple sclerosis, lupus or heart failure.[5-7] Furthermore, the need for regular self-injection poses a burden for patients. Lastly, the costs of these drugs are significant, both per patient per year (Europe $17,000, United States $26,000), as well as on a macroeconomic scale.[8,9]
These disadvantages might be ameliorated by dose reduction or discontinuation of TNFi after disease control has been achieved, and this indeed has been shown to be possible in a relevant proportion of patients.[10-12] A disease activity guided TNFi dose reduction strategy has been tested previously in the DRESS study (Dose REduction Strategy of Subcutaneous TNF inhibitors), and has been shown to be feasible and non-inferior to usual care with regard to prolonged flaring.[13] The strategy also did not result in differences in disease activity, functioning, quality of life, or relevant radiographic progression after 18 months. However, short lived flares and minimal radiographic progression occurred more frequently in the dose reduction arm, probably due to the temporary effects of unsuccessful dose reduction attempts on disease activity.[14] Although no benefits were seen with regard to side effects, the cost effectiveness was very high, reaching $440,000 saved per lost Quality Adjusted Life Year (QALY).[15]
Some important questions remain, especially with regard to long-term risks and benefits of this strategy. Does the occurrence of major flare remain comparable between groups after longer follow-up? Is the small difference in radiographic joint damage between groups only due to a temporary difference in disease activity, or should we expect more damage in subsequent years? And finally, can a lower risk of adverse events (e.g. infections) be demonstrated?
In an attempt to answer these questions, we performed an extension study of the original DRESS study, exploring long-term effects of this dose reduction strategy on disease activity, functioning, quality of life, radiographic progression and (serious) adverse events ((S)AE).

Methods

Study design and participants

This is a long-term extension study of the DRESS study, an 18 month, pragmatic, open label, randomized controlled, non-inferiority strategy trial in RA patients, in which a disease activity guided dose reduction (DR) strategy of adalimumab or etanercept was compared with usual care (UC). For inclusion criteria, we refer to Van Herwaarden et al, BMJ 2015. Disease activity was measured using DAS28-CRP (28 joint count based disease activity score with C reactive protein (CRP)).
The DRESS study was registered at the Dutch trial register (www.trialregister.nl, NTR 3216) and its design and results have been reported previously.[13-17] The extension study was performed from May 2014 to January 2016 in the Sint Maartenskliniek Nijmegen and Woerden, The Netherlands, and was approved by the local ethics committee (CMO region Arnhem-Nijmegen, NL37704.091.11).

Randomization and masking

In the intervention phase (month 0-18) of the DRESS study, patients were randomized to the DR or UC group in a ratio of 2:1, stratified for adalimumab and etanercept. In the extension phase (month 18-36) the original group allocation was maintained. Both the intervention and extension phase were non-blinded.

Procedures

In the intervention phase, patients allocated to UC continued a standardized tight control treatment protocol (maintaining DAS28-CRP <3.2).

In the DR group, patients received identical care, with addition of a specific dose reduction advice given to the treating rheumatologist for that particular patient. The DR strategy consisted of 3-monthly stepwise increase of injection time interval until flare or discontinuation. For details we refer to Van Herwaarden et al, BMJ 2015. If the flare persisted after 4 weeks despite bridging with intramuscular or intra-articular steroids or NSAIDs, TNFi was increased stepwise, if needed, to the shortest registered interval. If a flare persisted thereafter, treatment was switched. Only one dose reduction attempt was advised.

As flare criterion, a DAS28-CRP increase >1.2, or a DAS28-CRP increase >0.6 compared with baseline and current DAS28-CRP ≥3.2 was used (short-lived flares).[18] Major flare was defined as a flare persisting >12 weeks.

In the extension phase, the treatment strategies in both groups converged to the same strategy: treatment choices were left to the discretion of the treating rheumatologist and were based on local treatment protocols that included 1) disease activity measurement every three to six months and using treat-to-target to achieve at least low disease activity, 2) a preferential order of biologic Disease Modifying Anti-Rheumatic Drugs (bDMARDS) (see Appendix 1), and 3) a bDMARD dose optimization protocol (see Appendix 2). Patients originally allocated to UC were therefore also able to initiate TNFi dose reduction (Appendix Figure 1), but without specific dose reduction advices. After March 2015, DAS28-CRP cut-off levels for low disease activity and remission were slightly lowered to 2.9 and 2.4, as it was shown that DAS28-CRP thresholds should be slightly lower in comparison to DAS28-ESR.[19]

Outcomes

For the extension phase, the same endpoints were used as in the original DRESS study, although in an explorative, non-hypothesis testing manner. The primary endpoint was the difference in cumulative incidence of major flare between DR and UC group, during the extension phase and during the entire study (0-36 months).

Secondary endpoints were cumulative incidence of patients with short-lived flares, difference in Mean Time Weighted (MTW) DAS28-CRP score, MTW functioning, measured with the health assessment questionnaire-disability index (HAQ-DI), and quality of life at 36 months measured with EuroQol-5D-5L, proportions of patients in whom dose reduction or discontinuation was successful, bDMARD use, mean change (Δ) in Sharp-van der Heijde score (SvdH), and cumulative incidence and incidence density (ID) of (S)AE.

Successful dose reduction was defined as being on a lower dose than at baseline with concomitant low disease activity, measured both at 18 and 36 months. Successful discontinuation was defined as complete withdrawal of adalimumab or etanercept with concomitant low disease activity, measured both at 18 and 36 months.

In the extension phase, DAS28-CRP and HAQ-DI were measured at least every 6 months, and an EQ5D-5L was repeated at 36 months. For bDMARD use, the normalized proportion of the defined daily dose (DDD) was calculated with interquartile ranges (IQR) with 1.0 being the full dose equivalent.

Radiographs of hands and feet were obtained at 36 months and assessed using the modified SvdH score, by the same two blinded, trained readers that assessed the original DRESS radiographs. Scoring was done pairwise with radiographs from month 18 and 36 in known sequential order, but without rescoring baseline and 18 months, for efficiency reasons, as suggested for long-term studies.[20] Mean Δ in SvdH, and proportion of patients with ΔSvdH exceeding three different cut-off levels were compared between groups: 1) minimal clinical important change (MCIC) of eight points in 18 months,[21] 2) smallest detectable change (SDC)[22,23] and 3) 0.5 SvdH units for minimal radiographic progression.

Statistical Analysis

Stata IC v 13.1 was used. In the DRESS study, per protocol (PP) analyses were used for the primary outcomes because of the non-inferiority nature of the analyses. Because of 1) the more exploratory analyses in this extension phase, 2) difficulty defining "per protocol" when treatment decisions are left to the treating physician and 3) minor differences in PP and intention-to-treat (ITT) analyses in the original study, an ITT approach was chosen. Patients who did not give informed consent or were lost to follow-up before 24 months, were excluded. All analyses were done for the extension phase, and when appropriate for the entire study. Since previously no differences between TNFi (adalimumab or etanercept) were found, stratified analyses were deemed unnecessary for the extension phase.

For the primary analysis, we kept the original non-inferiority margin of 20% difference in major flare between DR and UC group, based on the same reasoning as mentioned before.[16] Point estimates with confidence interval (95% CI) of the difference in cumulative incidence of major flare between groups were calculated and the upper limits of the confidence interval were compared with the non-inferiority margin. A t-test compared mean/median medication use (MTW) DAS28-CRP, HAQ-DI and EQ5D-5L. Differences in cumulative incidence of flares, and levels of disease activity at 24, 30 and 36 months were compared by Chi-square testing. Different time points were tested separately, with no repeated measure analyses performed.

Role of the funding source

This study was funded by the department of rheumatology at the Sint Maartenskliniek Nijmegen, The Netherlands.

Results

Of 180 patients included in the DRESS study, 172 patients were enrolled in the extension phase: 115 patients in the DR and 57 in the UC group (Figure 1). Baseline characteristics at start of the extension phase were similar between groups, except for higher prevalence of csDMARD co-medication in the UC group (Table 1). The percentage of missing data was low: 2% of planned visits, and 2% to 8% missing per variable, therefore multiple imputation was deemed unnecessary and simple imputation using last observation carried forward in case the last observation was missing, or mean of previous and next were calculated for in-between missings.

Figure 1. Flow chart

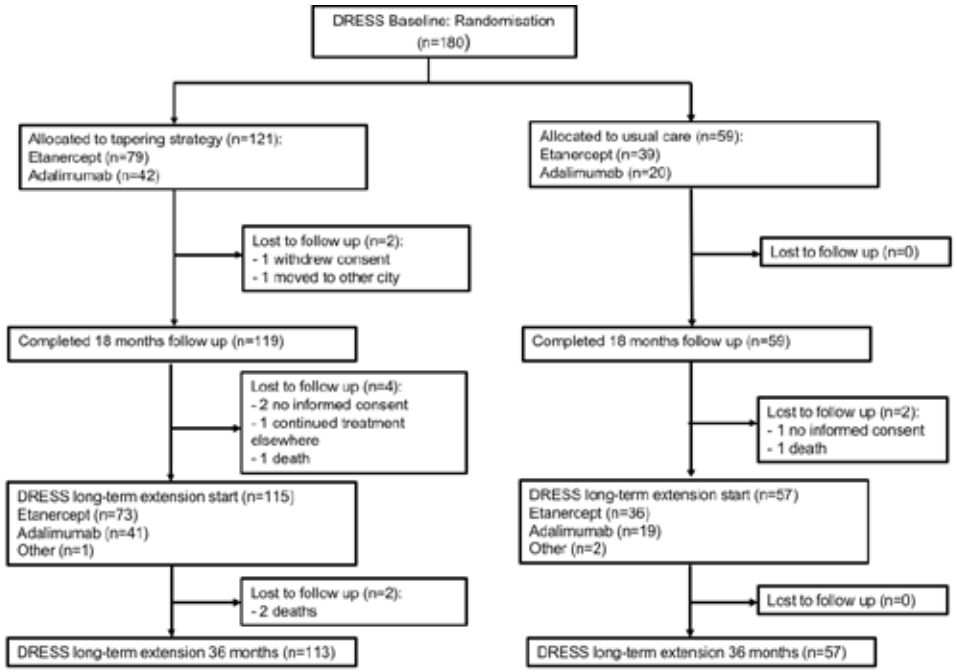


Table 1. Patient characteristics at DRESS baseline and at start of DRESS extension phase

	DRESS Baseline		DRESS extension	
	Dose reduction (n=115)	Usual care (n=57)	Dose reduction (n=115)	Usual care (n=57)
General characteristics				
Age, years (SD)*	59 (10.0)	58 (9.2)	60.9 (10.0)	59.7 (9.2)
Disease duration (years)†	10 (5-16)	10 (6-16)	11 (7-17)	12 (7-18)
SvdH score‡	21 (5.5-59)	19 (8.5-46.5)		
Female sex	71 (62)	39 (68)		
Diagnosis according to 2010 and/or				
1987 ACR criteria, n (%)	109 (95)	57 (100)		
Rheumatoid factor positive	90 (78)	47 (82)		
Anti-citrullinated peptide antibodies positive	82 (71)	44 (77)		
Erosive disease	94/112 (84)	52 (91)		
Disease activity characteristics				
No. of swollen joints†	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-0)
No. of tender joints†	0 (0-1)	0 (0-0)	0 (0-1)	0 (0-1)
Erythrocyte sedimentation rate (mm/h)*	17 (14)	16 (10)	20 (15)	16 (10)
C reactive protein (mg/L)*	4 (4)	4 (4)	7 (16)	4 (12)
DAS28-CRP score*	2.2 (0.7)	2.1 (0.8)	2.2 (0.9)	2.0 (0.9)
DAS28-ESR score*	2.5 (0.7)	2.5 (0.8)	2.7 (1.0)	2.5 (1.0)
2011 ACR/EULAR Boolean based remission	30 (26)	21 (37)	28 (23)	23 (39)
Treatment characteristics				
Etanercept/adalimumab/other	76/39 (66/34)	37/20 (65/35)	73/41/1 (63/36/1)	36/19/2 (63/33/4)
Duration of TNFi use at inclusion (years)*	3.5 (2.5)	3.5 (2.2)	5 (2.5)	5 (2.2)
Previous number of csDMARD treatments†	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
Previous number of TNFi treatments†	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Concomitant treatment				
csDMARD	68 (59)	45 (79)	69 (60)	40 (70)
Methotrexate	55 (48)	39 (68)	54 (47)	35 (61)
Methotrexate dose (mg)*	15.9 (5.7)	16.3 (5.6)	17.0 (6.5)	15.3 (5.0)
Glucocorticoids	3 (3)	3 (5)	6 (5)	6 (11)
NSAIDs	63 (55)	34 (60)	70 (61)	35 (61)

Data are number (%) of patients unless stated otherwise.
*Mean (standard deviation)
†Median (interquartile range)
‡n=101 in the dose reduction group, n=55 in the usual care group.
ACR/EULAR=American College of Rheumatology/European League Against Rheumatism. SvdH=Sharp van der Heijde score. DAS28-CRP=28 joint count based disease activity score with C reactive protein. DAS28-ESR=28 joint count based disease activity score with erythrocyte sedimentation rate. TNFi=tumor necrosis factor inhibitor. csDMARD=conventional synthetic disease modifying antirheumatic drug. MTX= Methotrexate; NSAIDs=non-steroidal anti-inflammatory drugs.

Flaring

The cumulative incidences of major flare during the extension phase were 12/115 (10%) in the DR and 7/57 (12%) in the UC group (difference -2%, 95% CI -8 to 15%). The upper limit of the 95% CI around the difference was <20%, compatible with non-inferiority of DR to UC group. The cumulative incidence from month 0-36 was 20/115 (17%) in the DR and 8/57 (14%) in the UC group (difference 3%, -10 to 15). There was no significant difference in cumulative incidence of short-lived flares during the extension phase: 49/115 (43%, 33 to 52%) in the DR and 20/57 (35%, 23 to 49%) in the UC group. From month 0-36, the cumulative incidence of flare remained different between groups: 96/115 (83%, 75 to 90%) in the DR and 25/57 (44%, 31 to 58%) in the UC group. Additional analyses within the DR and UC group on the occurrence of major and short-lived flares comparing adalimumab with etanercept, showed no significant differences in both the extension phase (18-36 months) as well as the whole study duration (0-36 months).

Disease activity, function and quality of life

In the extension phase, MTW-DAS28-CRP was 2.2 (SD 0.7) in the DR group and 2.1 (SD 0.7) in the UC group (difference 0.08, -0.15 to 0.30). MTW-DAS28-CRP from 0-36 months was 2.3 (SD 0.6) in the DR group and 2.1 (SD 0.7) in the UC group (difference 0.16, -0.03 to 0.35). DAS28-CRP, HAQ-DI and EQ5D-5L remained stable during the extension phase and complete follow-up, and were not significantly different between groups at any time point (Figure 2). Disease activity states were not significantly different between groups at any time point in the extension phase (Appendix Table 1).

TNFi tapering and medication use

In the intervention phase, 23/115 (20%, 13 to 28%) patients in the DR group had successfully discontinued their bDMARD, 52/115 (45%, 36 to 55%) successfully reduced their bDMARD and in 40/115 (35%, 26 to 44%) no dose reduction was possible. 19/115 (17%, 10 to 25%) patients in the DR group persisted being biologic-free with maintenance of low disease activity from the intervention phase until 36 months, and 33/115 (29%, 21 to 38%) of patients in the DR group persisted being successfully dose reduced from the intervention phase until 36 months.
During the intervention phase, 49/57 (86%, 74 to 94%) patients in the UC group did not attempt dose reduction (8 patients tapered or discontinued their bDMARD, mostly due to adverse events). In the extension phase, in 32/49 (65%, 50 to 78%) patients a dose reduction attempt was made. Of these, 19/49 (39%, 25 to 54%) were successfully dose reduced and 7/49 (14%, 1 to 27%) successfully discontinued at 36 months. In 12/32 (38%, 21 to 56%) patients in the UC group in whom a dose reduction attempt was made, a short-lived flare occurred. In patients in the UC group in whom a dose reduction attempt was made, 4 experienced a major flare. 2 of these patients reached low disease activity at the next visit after re-escalation or reinstallment. The remaining 2 patients had a major flare that was due to a high VAS score and high tender joint count. Re-escalation was thus deemed unnecessary by both the treating rheumatologist as well as the patient.
At study end, between group differences in numbers of patients successfully tapered or stopped were smaller but still existent (Figure 3).

Figure 2. Mean **A:** Disease activity (measured with DAS28-CRP) **B:** Functioning (measured with HAQ-DI) **C:** Quality of life (measured with EQ5D-5L)

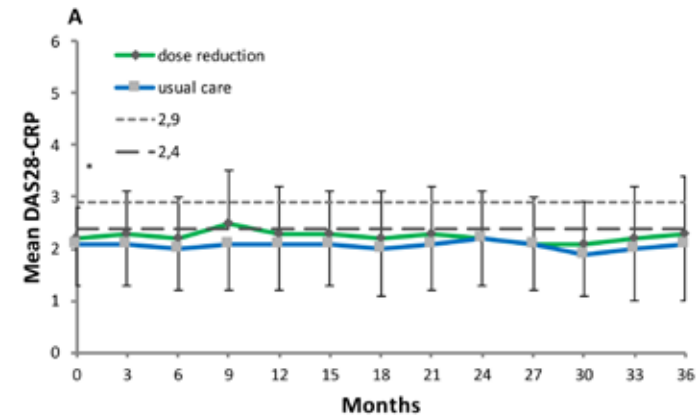
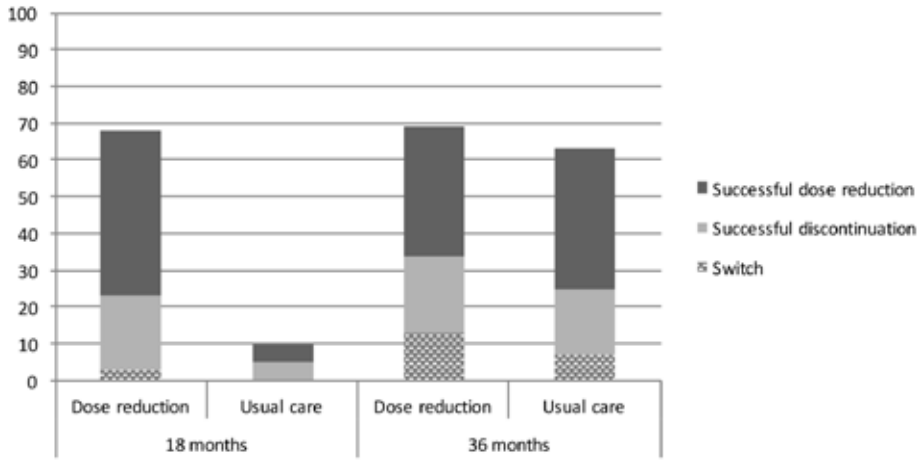


Figure 3. Dose optimization in dose reduction and usual care group (percentages) at 18 and 36 months



During the intervention phase, the proportion of the DDD of TNFi use was 0.50 (IQR 0.48 to 0.51) in the DR group and 0.92 (0.90 to 0.94) in the UC group (difference -0.42, -0.45 to -0.39). During the extension phase, this difference decreased but remained significant: 0.54 (0.51 to 0.58) in the DR and 0.67 (0.64 to 0.71) in the UC group (difference -0.13, -0.18 to 0.08). From 0-36 months, DDD was 0.53 (0.51 to 0.54) in the DR and 0.80 (0.78 to 0.82) in the UC group (difference -0.27, -0.30 to -0.25).

In the extension phase, no significant between-group differences in csDMARD use were observed. At 36 months, <10% of patients in both groups used oral steroids (difference -1%, -10 to 8%). During the extension phase, intramuscular or intra-articular glucocorticoid injections were given to 48/115 (42%, 33 to 51%) in the DR and 21/57 (37%, 24 to 51%) in the UC group, (difference 5%, -11 to 21%).

Radiological outcomes

156 patients (101 DR; 55 UC) had radiographs available at 18 and 36 months. No significant difference in mean progression score between groups was observed for the extension phase (Table 2). 2/101 (2%) patients in the DR group and no patients in the UC group exceeded the MCIC. No significant between-group differences were seen for the SDC (calculated as 5.1 points) or minimal radiographic progression as cut-off values.

Table 2. Radiographic outcomes

	Baseline to 18 months			18 to 36 months		
	Dose reduction (n=101)	Usual care (n=55)	Difference (95% CI)	Dose reduction (n=101)	Usual care (n=55)	Difference (95% CI)
Progression total SvdH	0.68 (1.5)	0.17 (1.1)	0.51 (0.06 to 0.97)	1.29 (2.4)	1.45 (2.2)	-0.16 (-0.93 to 0.62)
Progression erosion	0.26 (0.8)	0.13 (0.7)	0.13 (-0.13 to 0.39)	0.56 (1.3)	0.81 (1.6)	-0.25 (-0.71 to 0.21)
Progression JSN	0.43 (1.2)	0.05 (0.9)	0.38 (0.15 to 0.75)	0.73 (1.5)	0.64 (1.9)	0.09 (-0.46 to 0.64)
Progression > MCIC	0 (0%)	0 (0%)	0% (-8 to 4)	2 (2%)	0 (0%)	2% (-2 to 6)
Progression > SDC	5 (4%)	0 (0%)	4% (-4 to 10)	3 (3%)	3 (5%)	-2% (-9 to 4)
Progression > 0.5	37 (32%)	9 (15%)	17% (2 to 29)	50 (50%)	29 (53%)	3% (-20 to 13)

Progression = in units per 18 months. Data are mean (SD) or n (%). SvdH: modified Sharp-van der Heijde score; JSN: joint space narrowing; MCIC: Minimal Clinical Important Change (8 units); SDC: Smallest Detectable Change (5.1 units)

Safety

The cumulative incidence of AEs during the extension phase was equal in both groups: 39/115 (34%, 25 to 43%) in the DR and 22/57 (39%, 26 to 52%) in the UC group (difference -5%, -11 to 21) and the number of patients with SAEs was also not different between groups (difference 3%, -11 to 15). From month 0-36, 103/115 (90%, 82 to 94%) patients had an AE in the DR group and 54/57 (95%, 85 to 99%) in the UC group (difference -5%, -14 to 4%) and the number of patients with SAEs was different (difference 17%, 8 to 31%), caused by a higher incidence of elective surgery in the DR group. Overall, low IDs per 100 patient-years were observed for other SAE categories with no significant between-group differences (Appendix Table 2).

Discussion

To our knowledge, this is the first study investigating long-term effects of disease activity guided dose reduction of adalimumab and etanercept in RA patients. Results show that the initial efficacy and safety of this strategy are maintained. No relevant difference in the number of major flares could be demonstrated between DR and UC group, and disease activity, functioning and quality of life were also very similar. Furthermore, no significant difference in radiographic progression was found, although this might be caused by less contrast between groups, due to the converging treatment strategies. However, other benefits of tapering, including less adverse events (e.g. infections), were not observed.

There are some factors to take into account when interpreting our data. The design choices that were made for the extension study have advantages but also some drawbacks. Considering the latter, the convergence of strategies between groups and subsequent loss of

contrast, should lead to caution when interpreting the lack of differences between groups. The similarity in outcomes may be caused by the former dose reduction group doing well, but also in part by the original usual care group doing worse than before. However, the latter seems less likely, considering the very stable three year course in disease activity, functioning and quality of life. The outcomes are also highly comparable between the DR group from 18 to 36 months and the UC group from 0 to 18 months. Furthermore, in the extension phase of this study, flare criteria were altered since it was shown that cut-off values of DAS28-CRP for low disease activity and remission should be slightly lower than the validated flare criterion cut-offs using DAS28-ESR[19]. It is unclear, however, how this would have altered our results. Tight control would have become even more tight, but this would have occurred in both dose reduction and usual care group. Future studies should investigate how using different flare criteria influences treatment strategy outcomes.

On the other hand, the design of the study did allow to assess – in the former UC group - what level of TNFi dose reduction can be achieved when no specific dose reduction advice is given. Interestingly, in the majority of those patients an attempt to dose reduce was observed, and subsequent results were also comparable to those in the original DR group. This further supports generalizability of the results to clinical practice.

Although there was some drop-out during the extension phase, for the primary outcome, our study seems well powered. For analyses we did not power this study for, a type II error might be present. In the design of the original DRESS study, a sample size calculation showed that to be able to reject the null hypothesis in this study (i.e. the intervention is inferior compared to the control arm by more than the non-inferiority margin) with a power of 80%, and cccounting for a 10% drop-out, 180 patients in total were included. At the end of the long-term extension phase (month 36), 113 and 57 patients were still included. Thus this is only slightly below the numbers as calculated above and total drop-out is still below 10%.

Comparison of our findings to other long-term studies on disease activity guided dose reduction or discontinuation is difficult, due to paucity and heterogeneity of these studies, with different dose reduction strategies (e.g. interval lengthening vs. dose tapering, gradual vs. fixed dose reduction, or using different tapering schemes) and different definitions for relapse or flare.[10] A recently published paper of Raffeiner et al. is the only other study to show long-term (median follow-up 3.6 years) data from a prospective semi-randomized tapering trial.[24] However, only etanercept was studied and fixed dose halving was used instead of disease activity guided dose reduction versus continuation of etanercept. Reassuringly, the outcomes of this study were very similar to ours, with no significant differences in clinical outcomes and radiographic progression, albeit with much higher absolute baseline radiographic damage.

Two points are of interest with regard to adverse events, SAEs being more frequent in the dose reduction group and no observed benefits of TNFi tapering on risk for infections. Firstly, the higher incidence of SAEs seems an artefact, because it is almost exclusively caused by more elective surgery and SAEs that arose from study related PET/CT scanning, that was only done in the dose reduction group, resulting in information bias. Secondly, we were not able to demonstrate lower infection risks in the dose reduction group, which is in contrast to Raffeiner et al, and to what might be pharmacologically expected.[3] This difference in outcome might be caused by lower patient numbers and follow-up time, and less contrast between the treatment arms in the extension phase. Furthermore, duration of TNFi use before study start was much longer in our study and as patients susceptible to infections would have been more likely to have discontinued their bDMARD before inclusion, this could have led to selection bias (healthy survivor bias).

In conclusion, a disease activity guided dose reduction strategy of TNFi in RA patients doing well, seems a reasonable long term approach in RA treatment. Further optimization of this strategy could consist of identification of predictors for successful dose reduction or discontinuation, as this might prevent short-lived flaring.

Declarations and acknowledgements

Authors contributions

CB, NvH, FvdH, JF, RvV, HB, AvdM and AdB were involved in the study design. CB, NvH, AvdM, FvdH and AdB were involved in the data collection. CB, NvH, JF, AvdM and AdB performed the data analyses. All authors were involved in writing and revision of the manuscript. CB declares she had full access to all the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

HB received grants and personal fees from Pfizer and AbbVie, during the conduct of the study; grants and personal fees from Roche, BMS, MSD, UCB, all outside the submitted work.

RvV received grants from AbbVie, Amgen, BMS, GSK, Pfizer, Roche, UCB and personal fees from AbbVie, Biotest, BMS, Celgene, Crescendo, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, UCB, Vertex, outside the submitted work. JF received a research grant from BMS. AdB received congress invitations from Roche and Abvie and an expert witness fee from Amgen. The other authors declare that they have no conflicts of interest.

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2.1

APPENDIX 1: Local rheumatoid arthritis treatment protocol (Sint Maartenskliniek Nijmegen and Woerden, The Netherlands)

Reumatoid factor and anti-citrullinated peptide antibody (ACPA) negative and no erosions:

Week 0

Start with Methotrexate 15 mg every week subcutaneously, increase to 25 mg every week when tolerated.
Start with Hydroxychloroquine 400 mg every day.
Intramuscular steroids 120 mg single dose.

Week 6: DAS28-CRP ≥2.4 or ≥ 2.9 if RA diagnosis> 3 years ago:
Methotrexate 25 mg every week subcutaneously.
Hydroxychloroquine 400 mg every day.
Intramuscular or oral steroids.

Week 14: DAS28-CRP ≥2.9:
Leflunomide 20 mg every day.
Hydroxychloroquine 400 mg every day.

Week 26: DAS-28CRP ≥2.4 or ≥ 2.9 if RA diagnosis> 3 years ago:
Leflunomide 20 mg (or other sDMARD).
bDMARD (biologic disease modifying antirheumatic drug) no. 1*.
Intramuscular or oral steroids.

Week 39: DAS-28CRP ≥ 2.4 or ≥ 2.9 if RA diagnosis> 3 years ago:
Leflunomide 20 mg (or other sDMARD).
Stop Hydroxychloroquine.
bDMARD no. 2*.
Intramuscular or oral steroids.

After week 39: DAS-28CRP ≥ 2.4 or ≥ 2.9 if RA diagnosis> 3 years ago:
switch bDMARD according to the bDMARD preferential order (see below)*.

Reumatoid factor positive and/or anti-citrullinated peptide antibody (ACPA) positive and/or erosions and/or high disease activity at disease presentation

Week 0

Start with Methotrexate 15 mg every week subcutaneously, increase to 25 mg every week when tolerated.
Start with Hydroxychloroquine 400 mg every day.
Intramuscular steroids 120 mg single dose.

Week 6: DAS-28CRP ≥ 2.4 or ≥ 2.9 if RA diagnosis> 3 years ago:
Methotrexate 25 mg every week subcutaneously.
Hydroxychloroquine 400 mg every day.
Intramuscular steroids 120 mg single dose.

Week 14-16: DAS-28CRP ≥ 2.4 or ≥ 2.9 if RA diagnosis> 3 years ago:
Methotrexate 25 mg every week subcutaneously.
bDMARD no. 1*.
Intramuscular steroids 120 mg single dose.

Week 26: DAS-28CRP ≥ 2.4 or ≥ 2.9 if RA diagnosis> 3 years ago:
Methotrexate 25 mg every week subcutaneously.
bDMARD no. 2*.
Intramuscular steroids 120 mg single dose.

Week 39: DAS-28CRP ≥ 2.4 or ≥ 2.9 if RA diagnosis> 3 years ago:
Methotrexate 25 mg every week subcutaneously.
Stop Hydroxychloroquine.
Biological 3*.
Intramuscular or oral steroids.

After week 39: DAS-28CRP ≥ 2.4 or ≥ 2.9 if RA diagnosis> 3 years ago:
switch bDMARD according to the bDMARD preferential order (see below)*.

***bDMARD preferential order:**

If administration of a concomitant DMARD is possible

1. Etanercept
2. Adalimumab
3. Rituximab
4. Abatacept
5. Tocilizumab
6. Golimumab
7. Certolizumab
8. Infliximab

If administration of a concomitant DMARD is not possible

1. Tocilizumab
2. Etanercept
3. Adalimumab
4. Rituximab
5. Abatacept
6. Golimumab
7. Certolizumab
8. Infliximab

APPENDIX 2: local bDMARD dose optimization protocol (Sint Maartenskliniek Nijmegen and Woerden, The Netherlands)

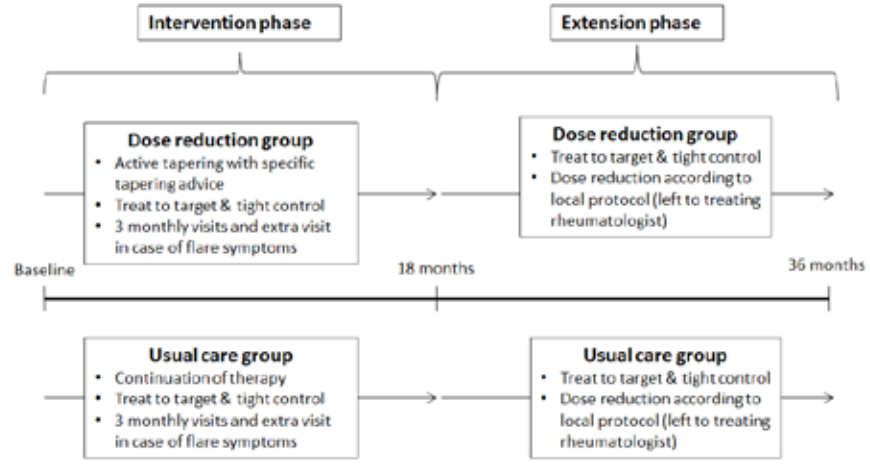
Baseline: start bDMARD

6 months: evaluate response criteria (DAS28-CRP <2.9 and decrease in DAS28-CRP >1.2).

1. **Response criteria are met:**
   - Start dose reduction according to predefined dose reduction steps.
     - o Etanercept:
       - From month 0 to month 6: once every 7 days 50 mg
       - Dose reduction step 1: 3 months once every 10 days 50 mg
       - Dose reduction step 2: 3 months once every 14 days 50 mg
       - Then discontinuation
     - o Adalimumab:
       - From month 0 to month 6: once every 14 days 40 mg
       - Dose reduction step 1: 3 months once per 21 days 40mg
       - Dose reduction step 2: 3 months once per 28 days 40 mg
       - Then discontinuation
   - Evaluation with DAS28-CRP measurement every 3 months with extra visits in case of flare symptoms (temporary bridging with steroids and NSAIDs is allowed).
   - Stepwise further dose reduction until discontinuation if no flare occurs.
   - In case of flare (DAS28-CRP increase >1.2 or DAS28-CRP ≥2.9 with DAS28-CPR increase >0.6) back to previous dose reduction step
2. **Response criteria are not met:**
   - Switch to another bDMARD

SUPPLEMENTARY DATA

Supplementary figure 1. Study conduct



Supplementary table 1. Disease activity states

	Dose reduction N=115	Usual care N=57
Baseline	N=115	N=57
DAS28-CRP<3.2	107 (93)	51 (89)
DAS28-CRP<2.6	86 (75)	46 (81)
Boolean	30 (26)	21 (36)
18 months follow up		
DAS28-CRP<3.2	100 (87)	51 (89)
DAS28-CRP<2.6	83 (72)	45 (79)
Boolean	27 (23)	23 (40)*
24 months follow up		
DAS28-CRP<3.2	96 (83)	47 (82)
DAS28-CRP<2.6	80 (70)	39 (68)
Boolean	33 (27)	21 (36)
30 months follow up		
DAS28-CRP<3.2	101 (88)	53 (93)
DAS28-CRP<2.6	87 (76)	47 (82)
Boolean	31 (27)	18 (31)
36 months follow up		
DAS28-CRP<3.2	92 (80)	48 (84)
DAS28-CRP<2.6	78 (68)	39 (68)
Boolean	30 (26)	15 (26)

* p = 0.005
Boolean based remission criteria: tender joint count, swollen joint count, CRP and patients' judgement of global disease activity using a visual analogue scale all ≤1.

Supplementary table 2. Safety summary

Cumulative incidences	Dose reduction (N=115)	Usual care (N=57)	Difference (95% CI)	Dose reduction (N=115)	Usual care (N=57)	Difference (95% CI)
	18 to 36 months			**0 to 36 months**		
Flares, N (%)						
Flare	49 (43)	20 (35)	8 (-9 to 23)	96 (83)	25 (44)	40 (25 to 53)
Major flare	12 (10)	7 (12)	-2 (-8 to 15)	20 (17)	8 (14)	3 (-10 to 15)
Other adverse events, N (%)						
Adverse events	39 (34)	22 (39)	-5 (-11 to 21)	104 (90)	54 (95)	-4 (-7 to 13)
Serious adverse events	22 (19)	9 (16)	3 (-11 to 15)	50 (43)	15 (26)	17 (8 to 31)
Deaths	2 (2)	0 (0)	2 (-5 to 6)	2 (2)	0 (0)	2 (-5 to 6)

Serious adverse events, incidence densities (95% CI)	Dose reduction (N=115)	Usual care (N=57)	Dose reduction (N=115)	Usual care (N=57)
	18 to 36 months		**0 to 36 months**	
Elective surgery	15.8 (9.8 to 21.8)	6.7 (1.4 to 12.1)	12.3 (8.7 to 15.9)	3.8 (3.5 to 4.1)
PET/CT related †	0.6 (0 to 1.7)	0	0.8 (0 to 1.7)	0
Infectious adverse event	2.5 (1.9 to 3.4)	2.3 (0 to 5.4)	4.2 (2.1 to 6.3)	2.2 (0.05 to 4.3)
Malignancy	4.7 (1.4 to 7.9)	0	3.1 (1.3 to 4.9)	1.1 (0 to 2.6)
Cardiovascular event	2.3 (0.03 to 4.6)	1.1 (0 to 3.3)	2.0 (0.5 to 3.4)	0.5 (0 to 1.6)
Pulmonary	0.6 (0 to 1.7)	2.2 (0 to 5.8)	0.6 (0 to 1.3)	1.1 (0 to 3.3)
Severe leucopenia	0	2.2 (0 to 5.8)	0	1.6 (0 to 3.5)
Gastrointestinal	1.2 (0 to 2.8)	1.1 (0 to 3.3)	0.6 (0 to 1.3)	0.5 (0 to 1.6)
Neurological	0	1.1 (0 to 3.3)	0.3 (0 to 0.8)	0.5 (0 to 2.6)
PMR	0.6 (0 to 1.7)	0	0.3 (0 to 0.8)	0.3 (0 to 0.8)
Allergic (injection) reaction	0	0	0	0

†In the dose reduction group only, patients were asked for participation in a study that involved PET/CT scanning. This sometimes yielded unexpected abnormalities.
ID: incidence density per 100 person-years; Dose reduction group= 171 observed person years for 18-36 months and 358 observed person years for 0-36 months; Usual care= 89 observed person years for 18-36 months and 182 observed person years for 0-36 months.

Chapter 2.2

Three year cost-effectiveness analysis of the DRESS study: protocolised tapering is key

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To be submitted

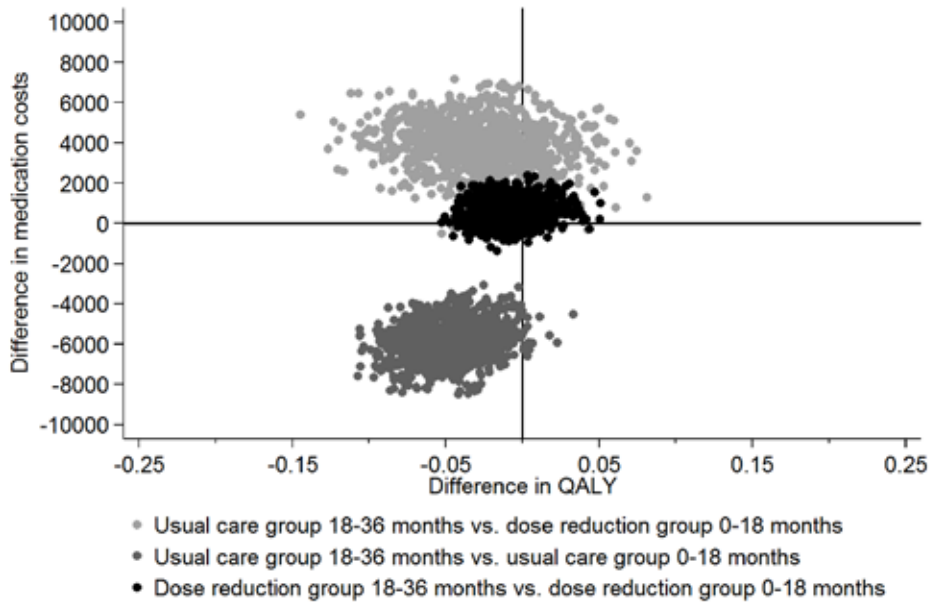
The DRESS (Dose REduction Strategy of Subcutaneous TNF inhibitors) study previously showed clinical non-inferiority and superior cost-effectiveness of disease activity guided tapering of tumour necrosis factor inhibitors (TNFi) (dose reduction, DR group) over full dose continuation (usual care, UC group) in rheumatoid arthritis (RA) patients with low disease activity.[1,2] Long-term extension data showed that safety and efficacy of this strategy were maintained up to three years with a large reduction in TNFi use.[3] While the fact that the majority of the UC group attempted dose reduction between 18-36 months prevented a valid comparison of disease activity guided tapering to full dose continuation over the entire study period, this study presented an opportunity to make the following comparisons:

1. Tapering long-term results (in DR group 18-36 months) vs. short-term results (in DR group 0-18 months)
2. Tapering at rheumatologist discretion (in UC group 18-36 months) compared to full dose continuation (in UC group 0-18 months)
3. Tapering at rheumatologist discretion (in UC group 18-36 months) compared to protocolised tapering (in DR group 0-18 months)

We previously reported the main results of the DRESS study (Dutch trial register, NTR3216), an open label non-inferiority randomised controlled trial (RCT) in which RA patients with low disease activity on a stable TNFi dose (adalimumab or etanercept) were randomised 2:1 to disease activity guided tapering or full dose continuation. In the first 18 months in the DR group, the TNFi dose was reduced stepwise until flare or TNFi discontinuation. In the extension phase, both groups were treated according to a treat-to-target protocol: tapering was recommended in case of stable low disease activity, at discretion of the rheumatologist in both groups. Visits were planned every 6 months, and assessments included disease activity (DAS28-CRP), quality of life (EQ5D-5L) and medication use.[1-3] Quality adjusted life years (QALY) were determined by trapezoid method. Since medication costs were the main cost drivers in the DRESS study, only medication costs were recorded from 18-36 months.
Results from 1000 bootstrapped replications concerning mean QALYs and total (biological and non-biological) medication costs for the 3 comparisons are presented in Figure 1 and Table 1. As shown, for the tapering strategy, costs are slightly but non-significantly higher after 18 months (higher in 86.3% of replications) with QALY being equal (lower in 66.2%, higher in 33.8% of replication, 0.007 (95% CI: -0.039 to 0.026) higher QALY for 0-18 months). Tapering at rheumatologist discretion is associated with lower cost (100% of replications) and slightly lower QALY (in 98.5%) compared to full dose continuation, but also with higher cost (in 99.7% of replications) and non-significantly lower QALYs compared to protocolised tapering (in 80.2%).

In conclusion, cost-effectiveness of protocolised tapering was maintained from 18 to 36 months, although medication costs rose slightly (ns), possibly because a subset of patients returned to a higher dose during follow-up. Tapering at rheumatologist discretion was less cost-saving than protocolised tapering and resulted in higher QALY loss than protocolised tapering, but is still cost-effective compared to full dose continuation.

Figure 1. Cost-effectiveness plane of the 3 comparisons made.



Comparisons within one treatment group are paired observations, and to take this into account for a more efficientanalysis, we bootstrapped $\overline{QALY\,(0\ to\ 18)}$ - $\overline{QALY\,(18\ to\ 36)}$ rather than $\overline{QALY\,(0\ to\ 18)}$ - $\overline{QALY\,(18\ to\ 36)}$ and likewise for cost.

Table 1. Summary of results for each comparison

Comparison	Difference in QALY	Difference in medication costs	Incremental net monetary benefit
Dose reduction 18-36 vs dose reduction 0-18	-0.007 (-0.039 to 0.026)	578€ (-575 to 1732)	-1104€ (-3819 to 1612)
Usual care 18-36 to usual care 0-18	-0.047 (-0.092 to -0.005)	-5940€ (-7764 to -4013)	2151€ (-1507 to 5571)
Usual care 18-36 vs. tapering 0-18	-0.028 (-0.096 to 0.043)	4013€ (1676 to 6199)	-6309€ (-12272 to – 280)

Positive QALY or iNMB and negative cost differences favour the group listed first. All figures are presented as mean (95% percentile based confidence interval); QALY: Quality adjusted life years; iNMB: incremental Net Monetary Benefit based on a willingness to pay of €80,000 per QALY. [4]

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Chapter 3

What causes a small increase in radiographic progression in rheumatoid arthritis patients tapering TNF inhibitors?

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Abstract

Objective

In a randomized controlled trial investigating tapering of TNF inhibitors (TNFi) compared with usual care in rheumatoid arthritis patients, minimal radiographic progression was more frequent in patients who attempted tapering. Possible explanations include higher incidence of flaring, higher mean disease activity, or lower TNFi use.

Methods

18-months data from the DRESS study were used. Change in Sharp van der Heijde (ΔSvdH) score (linear regression) and proportion of patients with >0.5 ΔSvdH (logistic regression) were used as outcomes. Cumulative incidence and number of short-lived and major flares per patient, mean time weighted disease activity (MTW-DAS28-CRP), and TNFi use were used as independent variables. Regression models were done stratified per study group and corrected for possible confounders.

Results

175 of 180 patients had 18-month data available. Mean ΔSvdH were 0.75 and 0.15 units with 37/116 (32%) and 9/59 (15%) patients exceeding 0.5 points in the tapering and usual care group respectively (both $p<0.05$). MTW-DAS28-CRP, but not incidence or number of short-lived or major flares, or TNFi use, was independently associated with mean progression score, but only in the tapering group. Additional analyses on DAS28-CRP subcomponents showed that this was mainly caused by MTW swollen joint count. No confounders were identified.

Conclusions

Radiographic progression was associated with higher MTW-DAS28-CRP (and especially swollen joint count), but only in patients that tapered TNFi. This finding stresses the importance of maintaining disease activity as low as possible in patients in whom TNFi is tapered and to check for radiographic progression regularly.

Keypoints

What is already known about this subject?

- The TNFi tapering strategy used in the DRESS study resulted in an increase in radiographic progression for patients that attempted tapering compared to patients that continued TNFi dosing.
- Although this increase was minimal over 18 months, it may become significant in subsequent years and lead to disability.

What does this study add?

- We investigated possible causes and found that higher disease activity (especially swollen joints) in combination with lower TNFi exposition was associated with mean radiographic progression.

How might this impact on clinical practice?

- This finding stresses the importance of maintaining a state of low disease activity or remission in patients in whom TNFi is tapered and to check for radiographic progression regularly.
- However, further progression in subsequent years is not to be expected, as higher disease activity is a temporary effect of a trial-and-error tapering strategy.

Introduction

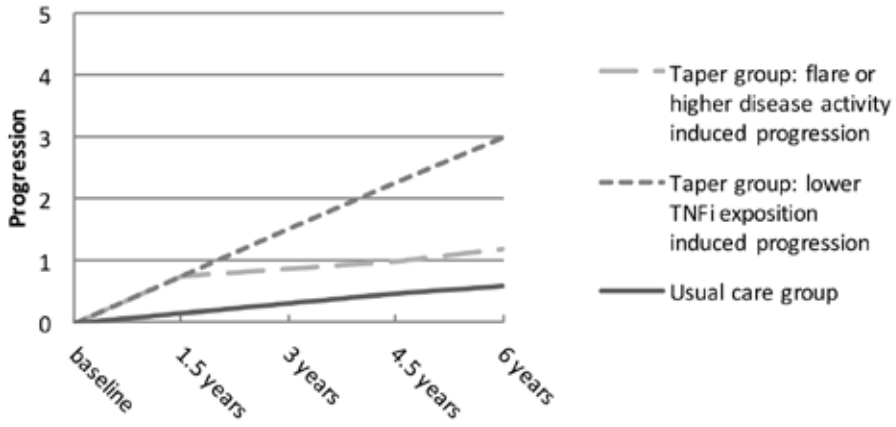
Disease activity guided tapering of TNF inhibitors (TNFi) in rheumatoid arthritis (RA) results in a significant reduction in TNFi use and subsequent cost, without compromising on important clinical outcomes(1). However, in the DRESS (Dose REduction Strategy of Subcutaneous TNF inhibitors) study a minimal increase in radiographic progression was observed for patients that attempted tapering compared to patients that continued TNFi dosing.

We propose three hypotheses that could explain this: firstly, in DRESS, short-lived flares were more frequent in patients tapering than in patients not tapering, which is a temporary effect of the trial-and-error type of tapering strategy. It could be hypothesized that the tapering strategy leads to a higher incidence of flares, thus causing radiographic progression(2). Secondly, a significantly higher mean time-weighted (MTW) disease activity was observed in the tapering group, again induced by the tapering and possibly resulting in radiographic progression. Thirdly, tapering causes lower TNFi exposition. Previous studies have suggested that TNFi use itself may prevent radiographic progression. Therefore, lower TNFi exposition could lead to progression, independent of increased disease activity(3-5).

These hypotheses have different clinical implications. In the first two hypotheses the effect is temporarily: progression is caused by a (sometimes unsuccessful) tapering attempt, not by lower TNFi use itself – so in subsequent years damage would not progress further. Tight control should be optimized, and if flares could be predicted, progression would be reduced. The third hypothesis would mean an ongoing process of radiographic progression in following years (Figure 1) and although the increase in progression that we found is minimal, it may become significant in subsequent years with consequent loss of function or pain symptoms. It would not be preventable by tight control alone and would require frequent radiographic monitoring and adaptation of TNFi use.

Therefore, we investigated the effects of the occurrence of short-lived or major flare, MTW disease activity and TNFi exposition on radiographic progression in patients tapering TNFi compared to patients not tapering.

Figure 1.



Patients and methods

Patients and definitions

Clinical and radiographic data from the DRESS study were used: an 18-month, open randomized clinical trial, investigating non-inferiority of a disease activity guided tapering strategy of adalimumab or etanercept compared to usual care (UC)[1,6].

Radiographs from baseline and 18 months were scored pairwise and in chronologic order using the Sharp-van der Heijde (SvdH) score by 2 researchers, blinded for clinical outcome and study group[7]. Absolute SvdH score with subcomponents and change (Δ) in SvdH score between baseline and 18 months were calculated. The proportion of patients with minimal progression, defined as ΔSvdH >0.5 points, was calculated. Additionally, proportions of patients exceeding the minimal clinically important change (MCIC) (8 points per 18 months, based on previous values of 4 points per year)[8,9] and smallest detectable change (SDC) (4.1 points)[1] were calculated.

Disease activity was defined using a 28 joint based disease activity score (DAS28) with C-reactive protein and MTW-DAS28-CRP was calculated over 18 months. For (short-lived) flare, a validated flare criterion was used: DAS28 increase of >1.2 compared with baseline, or DAS28 increase of >0.6 and current DAS28 ≥3.2[10]. A major flare was defined as a flare lasting >3 months. Cumulative incidence of patients with short-lived or major flare and number of short-lived or major flares per patient were calculated.

TNFi use was calculated in both the dose reduction and usual care group, as the normalized proportion of the defined daily dose (DDD) of TNFi, with 1.0 as full dose equivalent. DDD: 40mg/14 days for adalimumab and 50mg/7days for etanercept.

Statistical analyses

STATA/IC v. 13.1 was used. Descriptive statistics were done, (non) parametrically when appropriate. Univariate and multivariate analyses were performed with cumulative incidence and number of short-lived and major flares per patient, MTW-DAS28-CRP and TNFi use as independent variables. Both radiographic progression yes/no (ΔSvdH >0.5; logistic regression) and mean ΔSvdH (linear regression) were used as dependent variables. Possible confounders that were checked were: age, sex, body mass index, smoking, baseline SvdH score, DAS28-CRP, CRP, rheumatoid factor, anticitrullinated protein antibody status, oral glucocorticoid use and intramuscular or intra-articular glucocorticoid injections, number of glucocorticoid injections per patient and synthetic disease modifying antirheumatic drug use. To check for effect modification, all analyses were done stratified by allocation group (tapering or UC).

Results

Radiographic progression

175 (116 taper group/59 UC) of 180 patients had clinical and radiographic data available. Baseline characteristics were comparable between patients with missing and non-missing data.

Mean SvdH scores were 38.3 (SD 49.3) and 42.1 (58.7) at baseline (p= 0.65), and 39.0 (49.6) and 42.2 (58.7) at 18 months (p= 0.71) for the taper and UC group respectively (Table 1). Mean ΔSvdH over 18 months were 0.75 (1.5) and 0.15 (1.1) in the taper and UC group respectively (p<0.05). The difference in ΔSvdH between groups was mainly caused by joint space narrowing; change in erosion score was similar (Table 1). No patients exceeded the MCIC. The SDC was exceeded by 5 (4%) patients in the taper group and no patients in the UC group. Minimal progression was found in 37/116 (32%) and 9/59 (15%) patients in the taper and UC group respectively (p<0.05).

Table 1. Radiographic outcomes

	Taper group (n=116)	Usual care group (n=59)	Difference (95% CI)	Total (n=175)
SvdH baseline*	38.3 (49.3)	42.1 (58.7)	-3.79 (-20.4 to 12.8)	39.6 (52.5)
SvdH 18 months*	39.0 (49.6)	42.2 (58.7)	-3.19 (-19.9 to 13.5)	40.1 (52.7)
Progression SvdH score*	0.75 (1.5)	0.15 (1.1)	0.60 (0.16 to 1.0)	0.55 (1.4)
Progression erosion score*	0.29 (0.8)	0.12 (0.7)	0.17 (-0.07 to 0.42)	0.23 (0.8)
Progression joint space narrowing*	0.46 (1.2)	0.03 (0.9)	0.43 (0.07 to 0.78)	0.32 (1.1)
Progression >MCIC†	0 (0)	0 (0)	0 (0)	0 (0)
Progression >SDC†	5 (4)	0 (0)	5 (4)	5 (3)
Progression >0.5†	37 (32)	9 (15)	28 (17)	46 (26)

SvdH: Sharp-van der Heijde score; Progression SvdH: Sharp-van der Heijde progression between baseline and 18 months; MCIC: Minimal Clinical Important Change (8 units); SDC: Smallest Detectable Change (4.1 units); *Mean with standard deviation (SD); †Number (%)of patients.

Disease activity and (major) flare

MTW-DAS28-CRP was 2.3 (0.5) and 2.1 (0.6) in the taper and UC group respectively (p<0.01). For patients with minimal progression, median MTW-DAS28-CRP was 2.3 (interquartile range, IQR 2.0 to 2.8) in the taper group and 2.0 (1.9 to 2.4) in the usual care group. Additional data on mean DAS28-CRP at certain time points is provided in Supplementary Table 1. Short-lived flares occurred in 84/116 (72%) in the taper group and 16/59 (27%) in the UC group (p<0.001). Cumulative incidence of major flare was 14/116 (12%) and 6/59 (10%) in the taper and UC group respectively.

TNFi exposition

The median proportions of DDD were 0.47 (IQR 0.27-0.68) and 1.00 (IQR 0.95-1.00) in the taper and UC group respectively(p<0.0001). The lower bound of the IQR of the median proportion of DDD was slightly below 1.00 in the UC arm due to patients: discontinuing because of adverse events (n=6) or inefficacy (n=2); tapering because of low disease activity (n=5); being on lower than DDD dose at inclusion (n=2).

Regression modelling

Logistic regression with ΔSvdH >0.5 yes/no as dependent variable did not yield any association with short-lived or major flares, MTW-DAS28-CRP or TNFi use. In univariate linear regression with mean ΔSvdH as dependent variable, only MTW-DAS28-CRP, not occurrence of short-lived or major flares or TNFi use, was independently associated with progression (β= 0.51 (p= 0.005)). In multivariate analyses, only MTW-DAS28-CRP remained significantly associated with mean ΔSvdH. Effect modification was present by allocation group (Table 2), with a significant association between MTW-DAS28-CRP and progression in the taper group , but not in the UC group . Stratified corrected analyses for taper and UC group showed non-significant associations, except for MTW-DAS28-CRP. Additional exploratory analyses on subcomponents of DAS28-CRP showed that MTW tender and swollen joint count (MTW-TJ and MTW-SJ) were significantly associated with mean progression in the taper group. Patient global visual analogue scale (PG-VAS) and CRP were not significantly associated with mean progression (Table 2). Collinearity between MTW-TJ and MTW-DAS28-CRP was high (>0.7) but lower for MTW-SJ and MTW-DAS28-CRP, thus, MTW-SJ was added to the model. Afterwards, only MTW-SJ remained significantly associated with mean progression in the taper group with β=0.52 (95% CI 0.05 to 0.99)). No significant confounding was identified.

Table 2. Univariate linear regression models stratified by allocation group

	Tapering group		Usual care group	
	Beta	95% CI	Beta	95% CI
MTW-DAS28-CRP	0.64	**0.14 to 1.14**	0.17	-0.29 to 0.62
constant	-0.73		-0.20	
MTW-TJ	0.24	**0.07 to 0.10**	0.05	-0.13 to 0.24
MTW-SJ	0.65	**0.25 to 1.04**	0.21	-0.19 to 0.62
MTW-PG-VAS	0.02	-0.0001 to 0.38	0.004	-0.02 to 0.03
MTW-CRP	-0.001	-0.05 to 0.05	0.006	-0.03 to 0.05
Occurrence of flare	0.24	-0.38 to 0.87	0.091	-0.57-0.75
constant	0.58		0.13	
Number of flare per patient	-0.025	-0.34 to 0.29	0.041	-0.36 to 0.44
constant	0.78		0.14	
Occurrence of major flare	0.69	-0.16 to 1.53	0.82	-0.86 to 1.08
constant	0.67		0.14	
Number of major flare per patient	0.71	-0.06 to 1.47	0.11	-0.86 to 1.08
constant	0.66		0.14	
TNFi use (% ddd)	0.43	-0.65 to 1.51	-0.068	-1.38 to 1.25
constant	0.54		0.21	

95% CI: 95% confidence interval. MTW-DAS28-CRP: mean time-weighted DAS28-CRP. %ddd: percentage of the defined daily dose. TJ: tender joint count. SJ: swollen joint count. CRP: C-reactive protein. PG-VAS: patient global visual analogue scale.

Table 3. Final linear regression model stratified by allocation group

	Tapering group		Usual care group	
	Beta	95% CI	Beta	95% CI
MTW-DAS28-CRP	0.28	-0.30 to 0.87	-0.02	-0.70 to 0.65
MTW-SJ	0.52	**0.05 to 0.99**	0.23	-0.37 to 0.84
constant	-0.24	-1.5 to 1.01	0.07	-1.15 to 1.29

95% CI: 95% confidence interval. MTW-DAS28-CRP: mean time-weighted DAS28-CRP. SJ: swollen joint count.

3

Discussion

In this study, we investigated possible causes of the minimal difference in radiographic progression in RA patients tapering TNFi compared with usual care that was observed in the DRESS study. MTW-DAS28-CRP was the only variable significantly associated with progression, in the intervention arm of this study. Additional analyses on subcomponents of the DAS28-CRP showed that this was mainly caused by swollen joint count. Thus, it is the small overall increase in disease activity over time, and more specifically swollen joints, caused by the tapering strategy, and not the intermittent episodes of high disease activity (flares) that appear to cause progression. In patients that did not taper TNFi this association was not present. This suggests that radiographic progression occurs when both necessary causes (higher disease activity and lower TNFi exposition, which coincide in tapering), are present. Therefore, tight control - although also important in non-tapering patients - is even more important when tapering TNFi, to prevent additional progression. However, further progression in subsequent years is not to be expected, as higher disease activity is a temporary effect of a trial-and-error tapering strategy.

Our study has some limitations. Firstly, follow-up time of 18 months was limited. Furthermore, the level of radiographic progression that is of clinical relevance, is somewhat debatable. In 2006, Welsing et al established a level of 5 Sharp-Van der Heijde points per year as the minimal clinically important change[8]. This level may be different for the current RA population treated with more strict tight control. Therefore we also analyzed progression with different cut-off levels (SDC and minimal progression <0.5 SvdH points). Lastly, the observed SDC is relatively high and some misclassification of patients with progression that is actually due to measurement error could be present. However, this would cause bias towards a null result, whereas we did find differences in radiographic progression and in associations between disease activity and progression.

Our findings are in line with three studies that have shown some effect of discontinuation but no effect of tapering of TNFi tapering on radiographic progression in RA[11-13]. In the STRASS study, patients were randomized to disease activity guided TNFi tapering or continuation of treatment[11]. Multiple tapering attempts were allowed. A difference in disease activity and relapse rate was observed, but no difference in radiographic progression. Follow-up time and SDC were comparable to our study but sample size was smaller, which may explain why no progression was observed. In PRESERVE, patients were treated with etanercept and methotrexate for 36 weeks after which they were randomized to etanercept fixed dose halving, discontinuation, or full-dose continuation[12]. A significantly greater proportion of patients in the discontinuation group exceeded the SDC compared with patients continuing etanercept. This was explained by the fact that patients had moderate disease activity and were refractory to methotrexate monotherapy at study start. Furthermore, disease activity was not steered upon, leading to a significant rise in DAS28 after etanercept discontinuation. Lastly, Raffeiner et al. showed that randomization of RA patients in remission under etanercept, to either receive fixed halve dose etanercept or continuation of full dose etanercept, did not lead to differences in radiographic progression after two years[13].

In conclusion, disease activity guided TNFi tapering may result in a small increase in radiographic progression. This is possibly due to the disappearance of the direct inhibitory effect of TNFi on radiographic progression ('disconnect'), so that inflammation resumes driving this progression. These findings stress the increased importance of maintaining a state of low disease activity or remission – especially low swollen joint count – in patients in whom TNFi is tapered and to check for radiographic progression regularly. Long-term studies on TNFi tapering need to confirm that radiographic damage does not continue to progress over the years. Also, future studies should focus on predictors of successful tapering or discontinuation to further prevent the rise in disease activity that is the consequence of tapering.

Competing interests

A. den Broeder reports that he received a congress invitation from ABBVIE and ROCHE and received an expert witness fee from AMGEN, all outside the submitted work. The other authors have no competing interests to report.

Contributorship

CB, AdB, AvdM, FvdH and NvH were involved in the study design. CB, AdB, AvdM and NvH were involved in the data collection. CB, AdB, AvdM, RL, and NvH performed the data analyses. All authors were involved in writing and revision of the manuscript.

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Ethical approval

Ethical approval was given by the local ethics committee (CMO region Arnhem-Nijmegen; NL37704.091.11).

Data sharing

The authors commit to making the relevant anonymized patient level data available on reasonable request.

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Supplementary table 1. Mean DAS28-CRP values at baseline, 9 and 18 months and at flare visits

Mean DAS28-CRP	Dose reduction	Usual care	
	N=116	N=59	P value
Baseline	2.2 (0.6)	2.1 (0.7)	0.71
9 months	2.5 (1.0)	2.1 (0.9)	0.01
18 months	2.2 (0.9)	2.0 (0.9)	0.10
Flare visits	3.8 (0.7)	3.9 (0.7)	0.20

Chapter 4

Abatacept and tocilizumab tapering in rheumatoid arthritis patients: results of SONATA – a retrospective, explorative cohort study

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Abstract

Objectives

As data on disease activity guided dose optimization of abatacept and tocilizumab are scarce, we explored the feasibility, effectiveness and safety of dose optimization of these bDMARDs in rheumatoid arthritis (RA) patients in daily practice.

Methods

RA patients who were treated with abatacept or tocilizumab ≥ 6 months, with DAS28 <3.2 were included. Four groups were identified: abatacept dose reduction (DR) and usual care (UC), and tocilizumab DR and UC. Successful DR and discontinuation entailed being on lower dose than at baseline or having discontinued abatacept or tocilizumab, whilst maintaining DAS28 <3.2. Proportions of patients with successful DR or discontinuation at 12 months were described. DR maintenance was investigated using Kaplan-Meier curves. Between-group differences in mean DAS28 and HAQ-DI change (Δ) over 6 and 12 months were estimated.

Results

119 patients were included. DR was attempted in 13/28 (46%, 95% CI 28-66%) abatacept and 64/91 (70%, 60-79%) tocilizumab patients. At 12 months, 3/11 (27%, 6-61%) abatacept and 20/48 (42%, 28-57%) tocilizumab patients were successfully tapered. 1/11 (9%, 0-41%) abatacept and 5/48 (10%, 3-23%) tocilizumab patients were successfully discontinued. Mean ΔDAS28 and ΔHAQ-DI at month 6 and 12 were not significantly different between DR and UC. For tocilizumab, DAS28 was significantly higher in the DR compared to UC group at 6 months. Adverse events were comparable between groups.

Conclusion

Abatacept and tocilizumab DR appears to be feasible,and safe in clinical practice. No benefits in terms of fewer adverse events in the DR group were observed. Furthermore, DR was suboptimal, since all patients were eligible for DR but in a substantial number of patients, no DR was attempted.

Introduction

The advantageous effects of biologic disease modifying anti-rheumatic drug (bDMARD) treatment in rheumatoid arthritis (RA) on clinical, functional and radiographic outcomes have been well documented. However, bDMARDs are associated with adverse events (e.g. (serious) infections) and high costs[1,2]. With this in mind, dose optimization becomes important, which entails: 1) starting treatment when it is needed, 2) disease activity guided dose reduction to the lowest effective level when a patient is doing well, 3) discontinuing the drug when it is no longer required and 4) restarting or re-escalating in case of a flare. Disease activity guided dose reduction of tumor necrosis factor inhibitors (TNFi) in RA patients has proven to be feasible and safe[3-5] and has recently been included in RA management recommendations[6], however, data on disease activity guided dose optimization of non-TNFi bDMARDs are scarce.

Abatacept is a human fusion protein that selectively modulates the CD80/CD86:CD28 costimulatory signal required for full T cell activation. It is an effective treatment (either as monotherapy or in combination with a conventional synthetic DMARD (csDMARD)) in patients who are either csDMARD naïve or had an inadequate response to csDMARD or bDMARD[7-9]. Tocilizumab is a humanized monoclonal antibody directed against the Interleukin-6 (IL-6) receptor and is an effective treatment option after failure of a csDMARD or bDMARD, either as monotherapy or in combination with a csDMARD[10-13].

Few studies have been performed focusing on dose reduction or discontinuation of abatacept or tocilizumab[14-19]. With regard to abatacept, Takeuchi et al. observed abatacept-free remission in 22 of 34 (65%) patients after one year of discontinuation[15]. Furthermore, in the AGREE study, a double-blind randomized controlled trial, the efficacy of reduction of intravenous abatacept from 10 to 5 mg/kg in early RA patients was investigated[16], showing that the proportions of patients who lost DAS28-defined remission status were similar between groups at month[12]. Also, the AVERT study showed that in early RA patients reaching low disease activity after abatacept treatment for 12 months, radiographic benefits were maintained at 6 months after withdrawal of abatacept[17].

With regard to tocilizumab, Nishimoto et al. investigated discontinuation of tocilizumab in patients with early RA treated with tocilizumab monotherapy in the DREAM study[18]. Low disease activity was maintained in 35% after 6 months and in 13% after one year. Furthermore, the effects of dose reduction of tocilizumab were described in a small retrospective study in 22 patients[19]. Dose reduction was successful in 55% of patients after 6 months and all patients with worsening of disease activity after dose reduction regained low disease activity after dose escalation.

Thus, data on disease activity guided dose reduction of abatacept or tocilizumab in RA is limited. Moreover, most studies have focused on early RA patients enrolled in clinical trials, leaving uncertainty to its' feasibility in daily clinical practice. Therefore we aimed to retrospectively investigate the feasibility (including frequency of dose reduction attempts and persistence), effectiveness and safety of tapering of abatacept and tocilizumab in RA patients in daily practice.

Methods

Study design and participants

SONATA (Study ON Abatacept and Tocilizumab Attenuation) is a retrospective explorative mono-center controlled cohort study, investigating disease activity and functioning in RA patients that reached low disease activity on abatacept or tocilizumab treatment and attempted dose reduction, compared with control groups of patients that reached low disease activity on abatacept or tocilizumab treatment but never attempted dose reduction. All patients at the rheumatology department of the Sint Maartenskliniek, a specialized hospital in Nijmegen, The Netherlands, that had been or were still treated with either abatacept or tocilizumab were screened for eligibility. Patients were considered eligible if they were diagnosed with RA according to the 1987 and/or 2010 ACR criteria and/or clinical diagnosis by the treating rheumatologist and were treated at any time with abatacept and/or tocilizumab, reached low disease activity (DAS28-ESR <3.2) after 6 months of treatment and had at least 6 months of follow-up available.

Four cohorts were defined: abatacept dose reduction (DR) group, abatacept usual care (UC) group, tocilizumab DR group and tocilizumab UC group. Patients that attempted dose reduction because of low disease activity with or without adverse events were included in the DR group. Patients in whom DR was attempted solely because of adverse events were excluded. Patients who were eligible for DR but in whom no dose reduction attempt was undertaken (because of either patient or physician preference or unspecified reasons), were included in the UC group. Patients that were treated with both abatacept and tocilizumab were included in analyses only once for the first bDMARD used.

All patients eligible for inclusion were asked for written informed consent for retrospective data collection. According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands.

Procedures

Abatacept and tocilizumab were started, according to registration specifications: for abatacept either intravenously (i.v.) 500, 750 or 1000 mg/4 weeks depending on body weight, or subcutaneously (s.c.) 125 mg/week. Tocilizumab was administered either i.v. 8 mg/kg/4 weeks or s.c. 162 mg/week. Both were used as monotherapy or in combination with a csDMARD, preferably methotrexate.

Since 2010, a dose optimization protocol is being used in the Sint Maartenskliniek, which includes DAS28 steered dose reduction when DAS28 <3.2 is reached in longstanding RA patients for at least 6 months (or DAS28 <2.6 if RA is diagnosed <3 years ago). This is done by tapering the dose for i.v. bDMARDs and by increasing the interval for s.c. bDMARDs. For abatacept and tocilizumab, the following dose reduction regimens are used: 1) Abatacept i.v.: dose reduction of 250 mg every 3 months until discontinuation, or dose reduction of 250 mg every 6 months until discontinuation in patients with a baseline dose of 500 mg, 2) Abatacept s.c.: increasing the interval every 3 months, from 125 mg/7 days, to once every 10, 14 and 21 days, then discontinuation, 3) Tocilizumab i.v.: dose reduction every 3 months from 8 to 6 to 4 mg/kg /4 weeks, then discontinuation, 4) Tocilizumab s.c.: increasing the interval every 3 months, from 162 mg/7 days, to once every 10, 14 and 21 days, then discontinuation.

All treatment choices were left to the discretion of the treating rheumatologists. If symptoms of loss of disease control occurred, temporary treatment with Non-Steroidal Anti Inflammatory Drugs (NSAIDs) or steroids was advised. If a flare persisted, either according to a flare criterion (DAS28 increase of >1.2 or >0.6 with current DAS28>3.2)[20] or according to the judgement of the treating rheumatologist, the bDMARD was restarted or the dose was increased to the last efficacious dose. In case of persistently high disease activity, the dose was further reinstalled up to the registered dose, after which, if disease activity remained high, the bDMARD was switched.

Outcomes

Patient-, disease- and treatment characteristics were collected, as well as data on disease activity (28 joint Disease Activity Score using erythrocyte sedimentation rate (DAS28)) and functioning (health assessment questionnaire, HAQ-DI). Data was collected at start of abatacept or tocilizumab, at baseline (t=0) and every 3 months thereafter. Baseline was defined as being eligible for dose reduction. In the DR group this moment was set at initiation of dose reduction. In the UC group this moment was set at reaching low disease activity and using abatacept or tocilizumab for at least 6 months (theoretical time of start of dose reduction). Successful dose reduction and discontinuation were defined as having a lower dose or longer interval than at baseline or complete withdrawal of the bDMARD, respectively, with concurrent low disease activity (DAS28 <3.2). Follow-up time was 12 months for all outcomes, except for survival analysis using the maximal follow up until censoring or stopping of abatacept or tocilizumab.

Statistical analyses

STATA/IC v13.1 was used for all analyses. Descriptive statistics were used for demographic data and provided with mean (± standard deviation, SD) or median (interquartile ranges, IQR) depending on distribution. Proportions and 95% confidence intervals (CI) of patients in whom DR and discontinuation was considered successful at 12 months were described. Median time of persistence of successful dose reduction and discontinuation was calculated. A survival analysis was done using a Kaplan-Meier curve for time to re-escalation due to high disease activity in the DR group. Prevalence of patients switching to other bDMARDs within 12 months and reasons for switching were compared between the DR group and the UC group for both abatacept and tocilizumab. An unpaired t-test was used to assess differences in mean and mean change (Δ) in DAS28 and HAQ-DI at 6 and 12 months after becoming eligible in the DR versus UC group for abatacept and tocilizumab separately. Linear regression analyses for differences in DAS28 at 6 and 12 months between the DR and UC group were constructed to adjust for confounders specific for these outcomes. All baseline factors were checked for possible confounding. Because of low patient numbers in subgroups, abatacept and tocilizumab were combined in these analyses. Only factors that resulted in a change in beta >10% or (in case of too many factors relative to patient numbers) that were considered relevant were included in the final model. All factors were added to the model at once. Prevalence of pre-specified categories of serious adverse events were compared between the DR group and the UC group for both abatacept and tocilizumab. Frequencies of missing data were checked. In case of single missing values, single imputation was applied by last observation carried forward or calculation of the mean of the previous and next value. For linear regression analyses, missing baseline values were imputed using multiple imputation (10 times).

Results

Patients

From January 2007 until June 2015, 320 patients were treated with abatacept and/or tocilizumab, of whom 119 patients were considered eligible. Twenty-eight patients were using abatacept: 13 (46%) in the abatacept DR group and 15 (54%) in the abatacept UC group. Ninety-one patients were using tocilizumab: 64 (70%) in the tocilizumab DR group, and 27 (30%) in the tocilizumab UC group. Details and numbers of patients at follow-up are depicted in Figure 1. Patient characteristics at start of abatacept or tocilizumab and at baseline are depicted in Table 1. No large between group differences were observed. At baseline, mean duration of abatacept use was 1.1 years (SD 0.4) in the abatacept DR group and 0.7 years (SD 0.3) in the abatacept UC group. For tocilizumab, mean duration of tocilizumab use at baseline was 1.4 years (SD 0.4) in the tocilizumab DR group and 0.7 years (SD 0.3) in the tocilizumab UC group.

Figure 1. Flow chart with patient disposition (*abatacept/tocilizumab)

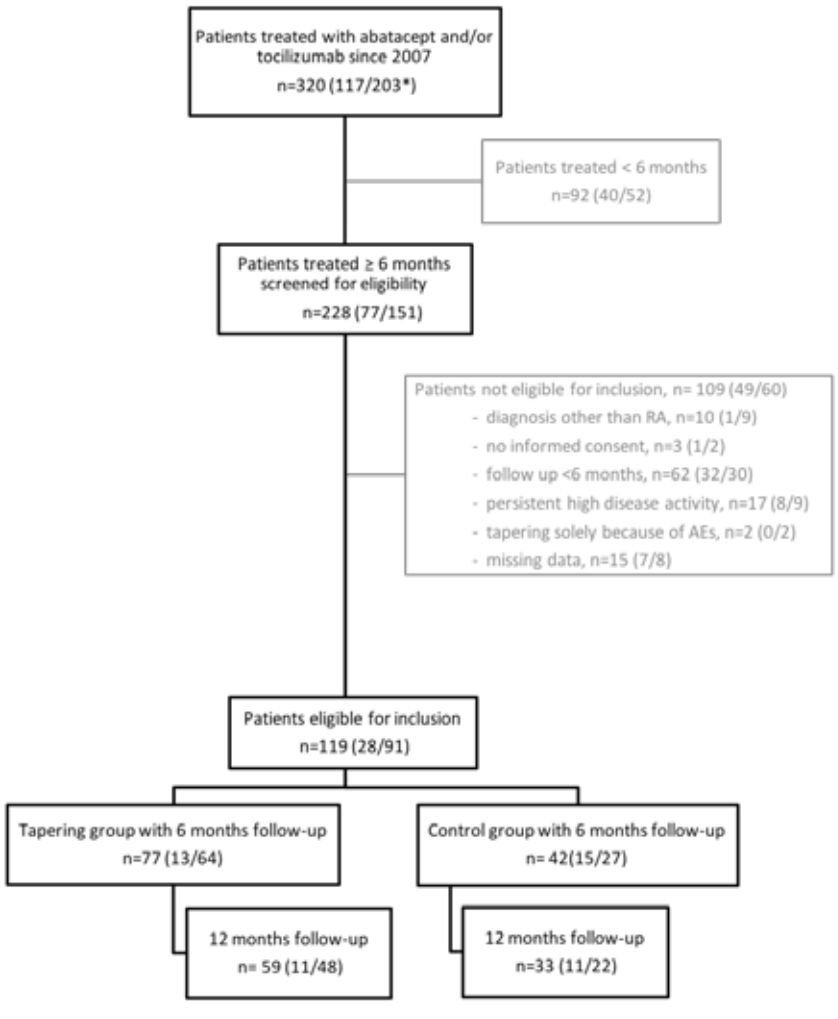


Table 1. Patient characteristics at start of abatacept or tocilizumab

	Abatacept DR (n=13)	Abatacept UC (n=15)	Tocilizumab DR (n=64)	Tocilizumab UC (n=27)
Age, years (SD)	59 (14)	59 (12)	61 (11)	55 (17)
Female, n (%)	12 (92)	14 (93)	47 (73)	19 (70)
Weight, kg (SD)	73 (16)	74 (9)	75 (18)	75 (15)
Disease duration, years median [p25-p75]	15 [10-18]	17 [12-21]	12 [5-16]	9 [2-16]
Rheumatoid factor positive, n (%)	12 (92)	12 (80)	51 (80)	19 (70)
Anti-CCP positive, n (%)	9 (69)*	12 (80)*	47 (73)*	17 (63)*
Erosive disease, n (%)	10 (77)*	9 (60)*	36 (56)*	10 (37)*
DAS28 (SD)	4.6 (0.9)	4.1 (1.4)	4.4 (1.2)	4.2 (1.1)
HAQ-DI (SD)†	1.8 (0.6)	1.5 (0.6)	1.5 (0.6)	1.7 (0.6)
I.v. administration, n (%)	11 (85)	9 (60)	56 (88)	19 (70)
S.c. administration, n (%)	2 (15)	6 (40)	8 (13)	8 (30)
Previous csDMARDs, median [p25-p75]	4 [3-5]	5 [3-6]	3 [2-4]	2 [2-3]
Previous bDMARDs, median [p25-p75]	4 [3-4]	4 [3-4]	3 [2-4]	3 [3-4]
Concomitant csDMARD, n (%)	7 (54)	6 (40)	30 (47)	17 (63)
Concomitant MTX, n (%)	4 (31)	5 (33)	11 (17)	10 (37)
Concomitant glucocorticoid, n (%)	5 (38)	9 (60)	45 (70)	17 (63)

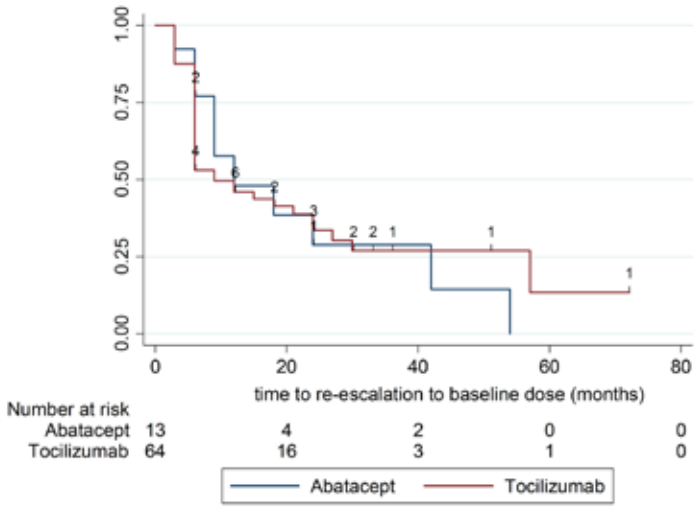
Anti-CCP: anti-cyclic citrullinated peptide; DAS28: 28 joints disease activity score- erythrocyte sedimentation rate; HAQ-DI: health assessment questionnaire – disability index; I.v.: intravenous; S.c.: subcutaneous; csDMARD: synthetic disease-modifying anti rheumatic drug; bDMARD: biologic DMARD; MTX: methotrexate. *Anti-CCP positivity: 14/119 (12%) missing data (2/13 abatacept DR; 2/15 abatacept UC; 8/64 tocilizumab DR; 2/27 tocilizumab UC). Erosive disease: 5/119 (4%) missing data (0/13 abatacept DR; 1/15 abatacept UC; 2/64 tocilizumab DR; 2/27 tocilizumab UC). †HAQ-DI: 33/119 (28%) missing data (4/13 abatacept DR; 3/15 abatacept UC; 21/64 tocilizumab DR; 5/27 tocilizumab UC).

Medication use

At 12 months, 3/11 (27%, 95% CI 6% to 61%) patients in the abatacept DR group were successfully tapered, with the i.v. dose being lowered by 50% in all 3 patients (from 750 mg to 375 mg i.v. every 4 weeks in 2 patients and from 500 mg to 250 mg i.v. every 4 weeks in 1 patient). For the tocilizumab DR group, 20/48 (42%, 95% CI 28% to 57%) were successfully tapered at 12 months, with the baseline i.v. dose of 8 mg/kg being lowered by to 6 mg/kg in 4 patients, to 5 mg/kg in 1 patient, to 4 mg/kg in 10 patients and to 2 mg/kg in 1 patient. For tocilizumab s.c., the dose was lowered from 162 mg/kg every 7 days to every 10 days in 1 patient, to every 14 days in 2 patients and to every 28 days in 1 patient. 1/11 (9%, 95% CI 0% to 41%) patients using abatacept and 5/48 (10%, 95% CI 3% to 23%) using tocilizumab were successfully discontinued. Of these

successfully tapered patients, in all 3 abatacept patients and in 12 tocilizumab patients, subsequent discontinuation could have been attempted, since these patients were having persistent low disease activity, but this was not done for unknown reasons. In 1/13 (8%, 95% CI 0% to 36%) patients in the abatacept DR group and 14/64 (22%, 95% CI 13% to 34%) patients in the tocilizumab DR group, more than one dose reduction attempt was made in the first 6 months after baseline. Median time of dose reduction with concurrent low disease activity was 6 months [p25-75 6-24) for abatacept and 9 months [6-18] for tocilizumab. Median time of discontinuation with concomitant low disease activity was 3 months for abatacept (n=1) and 3 [3-6] months for tocilizumab.
Figure 2 shows a Kaplan-Meier curve for time until re-escalation to baseline dose for both abatacept and tocilizumab, showing tapering was persistent up to 72 months.

Figure 2. Kaplan-Meier survival estimates until re-escalation to baseline dose for abatacept and tocilizumab



Hash marks indicate censored patients (end of follow-up)

In patients that attempted DR, 22/77 (29%, 95% CI 19 to 40%) patients that re-escalated again were having low disease activity at time of re-escalation. Of these, 1 patient using abatacept and 17 patients using tocilizumab re-escalated the dose because of a subjective increase in disease activity (more complaints, but no increase in swollen joint counts and ESR). Four patients using tocilizumab initially reduced the dose because of adverse events (in combination with low disease activity) and re-escalated again once the adverse event was resolved. None of the patients re-escalating ended up on a higher dose than at baseline. The median time to reach low disease activity again after re-escalation was 4.5 [3-6] months in the abatacept DR group and 3 [3-6] months in the tocilizumab DR group. In the DR group, 5/13 (38%, 95% CI 14 to 68%) patients using abatacept were ultimately switched to another bDMARD: 2 were switched due to secondary inefficacy after the dose reduction attempt, 2 were switched due to secondary inefficacy later on (after being back at baseline dose for a substantial amount of time) and 1 was switched due to adverse events. 13/64 (20%, 95% CI 11 to 32%) patients using tocilizumab were ultimately switched to another bDMARD: 2 were

switched due to secondary inefficacy after dose reduction, 8 were switched due to secondary inefficacy later on and 3 were switched due to adverse events. In the UC group, 2/15 (13%, 95% CI 2 to 40%) patients using abatacept were switched to another bDMARD, both due to adverse events. For tocilizumab, 4/27 (15%, 95% CI 4 to 34%) were switched to another bDMARD: 3 due to secondary inefficacy and 1 due to adverse events.

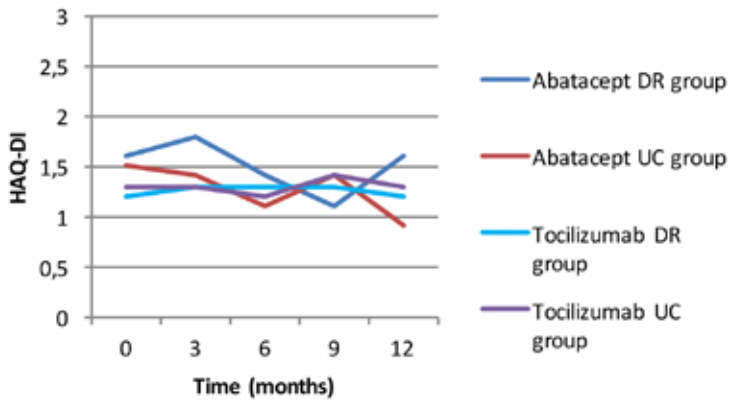
Disease activity and functioning

Mean ΔDAS28 and ΔHAQ-DI at month 6 and month 12 were univariately not significantly different between DR and UC groups in both abatacept and tocilizumab (Figure 3 and Supplementary table 1), although confidence intervals were wide especially for abatacept. Absolute DAS28 scores were univariately significantly higher for tocilizumab in the DR group than in the UC group at 6 months, but not at 12 months. No differences were seen for absolute DAS28 scores in the abatacept groups. However, adjusted for confounders no significant or relevant differences were seen for DAS28 course at 6 and 12 months: DAS28 difference adjusted for confounders (age, bDMARD (abatacept or tocilizumab), erosive disease, disease duration and DAS28 at baseline): +0.28 higher in DR group (-0.19 to 0.74) at 6 months and (adjusted for age, erosive disease, HAQ at start of the bDMARD, DAS28 at baseline) -0.34 lower in DR group (-0.98 to 0.29) at 12 months.

Figure 3a. Mean DAS28 for abatacept and tocilizumab DR and UC groups from baseline to month 12

Low disease activity defined as DAS28 <3.2

Figure 3b. Mean HAQ-DI for abatacept and tocilizumab DR and UC groups from baseline to month 12



Safety

In the DR groups, 4/13 (31%, 95% CI 9 to 61%) patients using abatacept and 38/64 (59%, 95% CI 46 to 71%) using tocilizumab experienced at least one adverse event. In the control groups, 2/15 (13%, 95% CI 2 to 40%) using abatacept and 14/27 (52%, 95% CI 32 to 71%) using tocilizumab experienced at least one adverse event. Incidence densities of different categories are depicted in Table 3, and were not significantly different between groups.

Table 3. Incidence densities of different adverse event categories per 100 patient years

Incidence densities	Abatacept DR	Abatacept UC	Tocilizumab DR	Tocilizumab UC
Infections	11 (2.2 to 31)	0	19 (12 to 29)	28 (14 to 51
Malignancies	0	3.8 (0.1 to 21)	1.5 (0.2 to 5.4)	5.1 (0.6 to 5.2)
Cardiovascular	0	3.8 (0.1 to 21)	1.5 (0.2 to 5.4)	0
Allergic reaction	0	3.8 (0.1 to 21)	0.7 (0.0 to 4.2)	2.6 (0.1 to 14)
Leucopenia	0	0	14 (8.5 to 22)	7.7 (1.6 to 23)
ALT increase	3.6 (0.1 to 20)	3.8 (0.1 to 21)	5.2 (2.1 to 11)	5.1 (0.6 to 19)
Surgery	7.1 (0.9 to 26)	7.7 (0.9 to 28)	0.7 (0.0 to 4.2)	2.6 (0.1 to 14.3)
Death	0	0	1.5 (0.2 to 5.4)	0
Other	11 (2.2 to 31)	7.7 (0.9 to 28)	9.7 (5.2 to 17)	10 (2.8 to 26)

Incidence density per 100 patient years. Abatacept DR: 28 observed person-years; abatacept UC: 26 observed person-years; tocilizumab DR: 134 observed person-years; tocilizumab UC: 39 observed person-years.

Discussion

To our knowledge, this is the first study to investigate the feasibility, effectiveness and safety of the implementation of a dose optimization strategy of abatacept and tocilizumab in RA patients in daily clinical practice. We could confirm that disease activity, functioning and safety were comparable between patients in whom a dose reduction attempt was undertaken and patients that never attempted dose reduction, with the exception of a significantly higher DAS28 at 6 months in the tocilizumab DR group as compared to the UC group. Furthermore, in the majority of patients that were successfully tapered at 12 months, the dosage was lowered at least 50% or the interval between injections was doubled (or longer). Also, dose reduction seems to be persistent in up to 30% of patients. However, the number of patients in whom dose reduction was attempted was lower than expected and tapering was not always done according to prespecified protocolised tapering steps. Also, in both the abatacept DR and UC group, mean DAS28 rose above the level of low disease activity during follow-up in contrast to tocilizumab where DAS28 remained low. We would like to discuss these findings in more detail.

We found that change in disease activity, functioning and safety were comparable between patients who tapered and patients who did not taper. This finding is comparable to other studies showing that tapering is feasible and safe in abatacept and tocilizumab [15,16,18,19,21-24] and to disease activity guided tapering in TNFi [3-5]. However, direct comparison of results is

hampered by the differences in tapering strategies (gradual tapering versus discontinuation without tapering first and dose lowering versus injection interval prolongation), criteria for successful tapering or discontinuation (low disease activity versus remission and necessity to use steroids or csDMARDs), open label versus blinded tapering, and follow-up time used in the studies.

The number of patients in whom a dose reduction attempt was undertaken was lower than expected, considering that all included patients were eligible for dose reduction. Furthermore, in the DR groups, duration of abatacept and tocilizumab use before a dose reduction attempt was made was much longer than in the UC groups. A reason for these low numbers and longer time before tapering could be timing. Dose reduction protocols have only been fully implemented in our clinic since 2014. Although dose reduction was done multiple times in trial settings in our clinic, it could be postulated that the absence of an outpatient clinic protocol and lack of experience with dose reduction outside of trial settings in the early years may have led to doctors being hesitant to dose reduction. Furthermore, in contrast to subcutaneous TNFi, where tapering consists of injection interval prolongation, dose reduction by lowering the dose has less obvious advantages to a patient, as the number of infusions needed remains the same. Thus, patients may have been more motivated to attempt dose reduction after subcutaneous abatacept and tocilizumab have become available. This argument is supported by a recent study showing that tapering of subcutaneous tocilizumab by injection spacing was more successful than tapering of intravenous tocilizumab by reduction of the dose [25]. Another possible explanation for the low percentage of dose reduction attempts is the fact that abatacept and tocilizumab were initially reserved for RA patients being refractory to other bDMARDs. Selection of a worse patient population may induce hesitation from patients and physicians to attempt tapering, when improvement in disease activity has proven to be a difficult goal to reach in the first place. This might especially be true for discontinuation attempts, which were not done in the majority of DR patients. Finally, patients might have negative expectations about dose reduction which may cause hesitation to dose reduce or induce negative symptoms during dose reduction, the so-called nocebo response [26,27]. All these factors are 'real world' issues and future studies should investigate these facilitators and barriers for dose optimization.

Remarkably, we observed a rise in disease activity above the level of low disease activity in both abatacept groups during follow-up, where DAS28 remained below low disease activity in both tocilizumab groups. An explanation could be that in our center, abatacept patients are more refractory to treatment than tocilizumab and thus a (small) rise in disease activity may be accepted more often than in patients using tocilizumab. It could also be that DAS28 is underestimated in the tocilizumab groups due to the inhibitory effects of tocilizumab on inflammation parameters. However, this would be most noticeable in DAS28-CRP whereas we used DAS28-ESR. All in all, the apparent rise in disease activity in abatacept patients might constitute a spurious finding , explained by small patient numbers in the abatacept groups as compared to the tocilizumab group.

With regard to adverse events, we expected to find a lower incidence of adverse events in the DR groups, especially fewer infections, but cumulative incidences were comparable with the UC groups. This may be explained by the retrospective, explorative design of this study (with probable underreporting of less severe adverse events) and the small numbers of patients in the subgroups. However, leucopenia was observed more often in both tocilizumab groups, which is a well-known adverse event of this bDMARD and this may suggest that adverse events were reported properly. We did not, however, investigate radiographic progression,

which would have provided further data on safety of tapering of abatacept and tocilizumab, especially in the long term.

Lastly, successful dose reduction appears to be persistent in this study. A recent study reported persistent response up to 2 years in patients prolonging the tocilizumab interval from 4 to 5 or 6 weeks [28]. Other studies reported outcomes with fixed follow-up time of 6 to 18 months[15,16,18,19,21-24], and our study adds that successful dose reduction or discontinuation persists up to 72 months in a subset of patients. Although we did not investigate medication cost, one may infer that this is associated with a significant cost reduction.

Our study has some important limitations. Firstly, due to the relatively small patient numbers, confidence intervals are large and results should be interpreted with caution. Of course, although superiority tests could not demonstrate differences, this cannot be interpreted as proof of equivalence, as the latter needs comparison of the confidence interval with an a priori chosen non-inferiority margin. Furthermore, at baseline, the prevalence of concomitant csDMARD use was low. However, abatacept and tocilizumab are equally effective as monotherapy compared to combination therapy, and indeed are registered in the USA as such[29,30]. Furthermore, at least for tocilizumab it is shown that tapering is equally successful in patients with and without concomitant methotrexate [23]. Also, concomitant csDMARD use has been shown not to be a predictor for successful dose reduction [30].

In contrast to most other studies, we used low disease activity (DAS28 <3.2) instead of remission to define successful dose reduction or discontinuation. This was done since remission is only reached in 30-80% of patients [32-35], because remission is not always attainable, and because protocol adherence of a physician to adjust medication in case disease activity rises above remission level is suboptimal (around 65%) [36], reflecting discordance with this strict goal. Furthermore, lower disease activity before tapering has not shown to be a predictor for higher chance of successful tapering [31].

All in all, dose optimization of abatacept and tocilizumab in daily clinical practice appears to be feasible and safe in a clinical practice setting. However, no benefits in terms of fewer adverse events in the dose reduction groups were yet observed. Future research should provide further information on possible predictors of successful dose reduction, long-term effects of dose optimization of these drugs, as well as the risk of radiographic joint damage. Furthermore, protocol adherence may be improved by research on possible facilitators and barriers of dose optimization.

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Conflicts of interest

CB, LT, DH, CvdE and AvdM have no conflicting interests to report. AdB was expert witness for Amgen and Boeringer Ingelheim, had congress visits with Pfizer, cellgene and Abbvie, and received research grant from BMS.

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4

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Chapter 5

Prediction of successful tapering or discontinuation

Chapter 5.1

A multi-biomarker score measuring disease activity in rheumatoid arthritis patients tapering adalimumab or etanercept: predictive value for clinical and radiographic outcomes

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Abstract

Objective

To evaluate the predictive value of the baseline multi-biomarker disease activity (MBDA) score in long-standing rheumatoid arthritis (RA) patients with low disease activity tapering tumor necrosis factor inhibitors (TNFi) for successful tapering or discontinuation, occurrence of flare and major flare, and radiographic progression.

Methods

DRESS (Dose REduction Strategies of Subcutaneous TNF inhibitors; Dutch Trial Register, NTR 3216) is 18-month non-inferiority RCT comparing tapering of TNFi until discontinuation or flaring with usual care (UC) in long-standing RA patients with stable low disease activity. Flare was defined as DAS28-CRP increase >1.2 or >0.6 if current DAS ≥3.2; major flare was a flare lasting >3 months, despite treatment intervention. MBDA scores were measured at baseline. Radiographs were scored at baseline and 18 months using the Sharp-van der Heijde score (SvdH). Area Under the Receiver Operating Characteristic curve (AUROC) was used to analyze the capability of baseline MBDA score for predicting the above-mentioned outcomes.

Results

Serum samples and outcomes were available for 171 of 180 patients from DRESS (115 tapering; 56 UC). AUROC analyses showed that baseline MBDA score was not predictive for the above-mentioned clinical outcomes in the taper group, but did predict major flare in the UC group (AUROC 0.72, 95% CI 0.56-0.88). Radiographic progression was minimal and was not predicted by MDBA score.

Conclusion

In this disease activity-guided strategy study of TNFi tapering in RA patients with low disease activity, baseline MBDA score was not predictive for successful tapering, discontinuation, flare, major flare or radiographic progression in patients who tapered TNFi.

Key messages

- Predictors for successful tapering or discontinuation of TNFi in RA patients are needed.
- The multi-biomarker disease activity score showed low to moderate correlations with DAS28-CRP in this long-standing RA population.
- The multi-biomarker disease activity score did not predict flare-related outcomes in this disease activity-guided TNFi tapering trial.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that requires frequent monitoring of disease activity to achieve tight control by setting a treatment target and changing treatment accordingly[1]. The disease activity score (DAS28), based on erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), is currently the most widely used measure of RA disease activity[2]. In either version, DAS28 is a composite measure that includes 28 tender and swollen joint counts, patient global assessment by visual analogue scale and a laboratory measure of inflammation.

Although use of the DAS28 for treating-to-target has been extensively validated, there are possible drawbacks to DAS28, as for any composite disease activity measure. Clinical assessments are subject to interobserver variability, resulting in measurement error and suboptimal precision[3,4]. Also, DAS28 can be influenced by other factors than RA disease activity (e.g. osteoarthritis, fibromyalgia or other causes of inflammation, such as infection) resulting in clinical misclassification of disease activity state. Additionally, ongoing subclinical disease activity can cause long-term damage in RA patients who are classified as having low disease activity or remission according to DAS28[5]. Finally, joint examination requires face-to-face contact and time with trained personnel, which may hamper feasibility in some settings. It would thus be desirable to have tools that are more objective and convenient than those currently used for measuring RA disease activity. Biomarkers could be promising candidates.

Biomarkers have the potential for smaller measurement error than clinical measures, and measuring serum markers may be less costly and more feasible than face-to-face contact with full joint counts. Biomarkers could potentially be better for detecting subclinical disease activity and, consequently, predicting risk for radiographic damage. Potential drawbacks of serum biomarkers include laboratory measurement error and misclassification, as biomarker levels may sometimes be affected by other factors than RA[6,7]. Lastly, despite the inherent desirability of objective measurement, it is currently expected that for a measure of RA disease activity to have good face, content and construct validity, it needs to include a patient perspective on disease activity. This approach contrasts with the reductionist laboratory measurement approach, although both approaches may be complementary.

The multi-biomarker disease activity (MBDA) blood test combines the serum concentrations of 12 protein biomarkers in an algorithm, to provide a score that quantifies RA disease activity on a scale of 1–100. The MBDA score was designed to correlate with DAS28-CRP, although the two can be discordant[8–10]. The MBDA score often detects elevated disease activity when DAS28-CRP or CRP do not[11–13]. In a study of RA patients receiving ongoing treatment with non-biologic disease modifying anti-rheumatic drugs (DMARDs) (median disease duration 4.6 years), including those in remission or with low disease activity, the MBDA score was a stronger predictor of future radiologic progression than the DAS28-CRP[11,12]. In patients with

early RA initiating methotrexate (MTX) treatment, the MBDA score predicted development of radiographic progression[13] independently of DAS28. It therefore seems possible that the MBDA score may be complementary to conventional clinical disease activity assessments.
Treatment strategies in established RA are shifting toward dose optimization, which includes dose tapering of biologic DMARDs (bDMARDs) when remission or low disease activity is reached. Hitherto, no predictive factors for treatment reduction have been validated. Thus, the MBDA score may potentially be of help in identifying patients who could successfully taper or discontinue their bDMARD.
In the present study we therefore investigated the clinical utility of the MBDA score in patients with long-standing RA and low disease activity, who were randomly assigned to either taper their tumor necrosis factor inhibitor (TNFi) or continue treatment[14], by evaluating the capability of the MBDA score for predicting successful tapering and discontinuation, the occurrence of flare or major flare and radiographic progression.

Methods

Study population and design

Baseline serum samples and clinical and radiographic outcomes were used from the Dose REduction Strategy of Subcutaneous TNF inhibitors (DRESS) study (Dutch Trial Register, www.trialregister.nl, NTR 3216): an 18-month, open randomized clinical trial that investigated non-inferiority of a dose reduction strategy of adalimumab or etanercept compared with usual care[14]. The study was performed at the Sint Maartenskliniek in Nijmegen and Woerden, the Netherlands, from December 2011 through May 2014, and was approved by the local ethics committee (CMO region Arnhem-Nijmegen, NL37704.091.11). The ethical approval was for the DRESS study as well as the collection of serum samples and radiographs for future studies. No separate ethical approval was require for the current study. Consenting patients with RA (2010 American College of Rheumatology RA criteria and/or 1987 RA criteria and/or clinical diagnosis by the treating rheumatologist), treated with adalimumab or etanercept at a stable dose for at least 6 months and with stable low disease activity at 2 consecutive visits were included. Randomization took place by a research physician who allocated patients to the taper group or usual care group in a ratio of 2:1, using a randomization list generated by computer, stratified for adalimumab and etanercept.
All patients were treated according to tight control with visits scheduled every 3 months up to month 18. Starting at baseline, etanercept and adalimumab injection intervals were increased every 3 months in the dose-tapering group. For adalimumab, which was being administered at enrollment as 40 mg every 14 days, the steps were: 40 mg every 21 days starting from baseline, 40 mg every 28 days starting from month 3, then discontinuation at month 6. For etanercept, which was being administered at enrollment as 50 mg every 7 days, steps were: 50 mg every 10 days, 50 mg every 14 days, then discontinuation. In the control group patients were treated according to usual tight control care. If patients experienced worsening of disease activity, an extra visit was planned. Non-steroidal anti-inflammatory drugs (NSAIDs) and intramuscular and intra-articular steroids were allowed and a follow-up visit after 4 weeks was advised. In the case of a flare persisting after 4 weeks, the last effective TNFi dosing interval was reinstated; if no improvement of disease activity occurred, TNFi was increased stepwise, if needed, to the shortest registered interval[14]. If a flare persisted thereafter, treatment was switched. Only one attempt at tapering was made per patient.

Clinical measurements

The predictive value of baseline MBDA score was evaluated for five clinical outcome measures in three categories relevant to TNFi dose reduction: successful dose tapering or discontinuation; occurrence of flare or major flare; and occurrence of radiographic progression. Successful tapering was defined at 18 months as using the TNFi at a longer interval or lower dose than at enrollment, with concurrent low disease activity and absence of flare. Occurrence of a flare was defined according to a previously validated criterion: a DAS28-CRP increase of >1.2 compared with baseline or a DAS28-CRP increase of >0.6 compared with baseline and current DAS28-CRP ≥3.2[15]. Major flare was defined as a flare persisting >3 months. Thus, a flare was defined prior to administration of any treatment for the flare, whereas a major flare was defined after up to 3 months of such treatment. For patients with multiple flares, only the first flare was considered for analyses.

Biomarker measurement and the MBDA test

Serum samples were collected at baseline, processed within 2 hours after blood collection and stored in standard separator tubes at −80°C. One or two freeze-thaw cycles were required to prepare the samples for shipping. All samples were shipped frozen to Crescendo Bioscience (South San Francisco, California, USA) for MBDA testing in the CLIA certified laboratory that is used for the Vectra® DA test. The 12 biomarkers that were measured are: VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, leptin, resistin, SAA and CRP. The MBDA algorithm combines the concentrations of these 12 biomarkers to generate a score on a scale of 1 to 100, with validated categories of <30 for low disease activity, 30–44 for moderate, and >44 for high disease activity[6,10,16].

Radiography

Standard radiographs of hands and feet were obtained at baseline and after 18 months. Sharp van der Heijde (SvdH) scoring was performed by 2 trained observers, who evaluated X-rays in chronological order and were blinded to the occurrence of flares and medication use. Radiographic progression was defined as change in SvdH >0.5 point from baseline to month 18[17]. The calculated smallest detectable change in SvdH was 4.1 points. For exploratory analyses, radiographic progression was evaluated using definitions of change in SvdH >3 points and change in SvdH >5 points.

Statistical analyses

Descriptive statistics were done parametrically or non-parametrically, as appropriate, and mean DAS28-CRP and mean MBDA scores at baseline were calculated. Correlations between baseline MBDA score and DAS28-CRP and its subcomponents were assessed by Spearman's ρ. Disease activity categories (low, moderate and high) according to DAS28-CRP and MBDA score were cross-classified. Agreement was calculated using quadratic weighted Cohen's κ. Categories used for DAS28-CRP were <2.7 for low disease activity, 2.7–4.1 for moderate disease activity and >4.1 for high disease activity[18].
All analyses were performed for all patients combined and by randomization group, with the exception of those analyses of successful tapering and successful discontinuation (which apply only to the tapering group) and sensitivity analyses of radiographic progression by 3 or 5 SvdH points (performed only for all patients combined). Analyses of Area Under the Receiver Operating Characteristic curve (AUROCs) were used to evaluate the predictive value of baseline MBDA score for successful tapering, successful discontinuation, flare, major flare

5.1

and radiographic progression. Kaplan-Meier curves were generated for the time to flare using baseline MBDA score categories. Cumulative probability plots were generated to display radiographic progression for each baseline MBDA category. Characteristics of patients with and without missing data were compared. Afterwards, patients with missing data were excluded from further analyses.

Results

Patient baseline characteristics

180 patients participated in the DRESS study, with 121 patients randomized to dose tapering and 59 patients to usual care. Of these patients, 171 (115 tapering, 56 usual care) had baseline and outcome measures available, eight patients had no baseline serum sample and one patient had no 18-month clinical outcome data. Baseline characteristics were comparable between patients with and without missing data. For the 171 patients in the present analyses, mean age was 59.0 years (standard deviation [SD] 9.7), 63% were female and median disease duration was 10 years (25–75 percentile, 6–16) (Table 1). Mean baseline DAS28-CRP was 2.16 (SD 0.68) and mean baseline MBDA score was 33.7 (SD 12.3) (Table 2).

Outcomes related to tapering and flare

At 18 months, 19% (22/115) of patients in the taper group had successfully discontinued TNFi, 44% (51/115) had successfully tapered the dose and 37% (42/115) were not able to taper the dose. Flares occurred in 99/171 (58%) patients, with 84/115 (73%) in the taper group and 15/56 (27%) in the usual care group (odds ratio, OR 7.4, 95% CI 3.6-15.2). Major flare occurred in 20 of 171 patients (12%), with 14/115 (12%) in the taper group and 6/56 (11%) in the usual care group (OR 1.2, 95% CI 0.4-3.2).

Rates of radiographic progression

Baseline serum samples and radiographic data at baseline and 18 months were available for 167 patients. Median SvdH scores at baseline were 23 and 17.5 in the taper and usual care groups, respectively (14). Mean (SD) change in SvdH score was 0.71 (1.5) in the taper group and 0.22 (1.5) in the usual care group. Radiographic progression (change in SvdH >0.5) occurred in 43/167 (26%) patients: 34/111 (31%) in the taper group and 9/56 (16%) in the usual care group. In the total group, 10/167 (6%) had change in SvdH >3 and 4/167 (2%) had change in SvdH >5.

Table 1. Baseline characteristics

	Total (N=171)	Tapering (N=115)	Usual care (N=56)	P value
Demographics				
Age, years, mean (SD)	59.0 (9.7)	59.5 (9.9)	58.0 (9.3)	0.34
Female, n (%)	108 (63)	70 (61)	38 (68)	0.38
Current smoking, n (%)	43 (25)	25 (22)	18 (32)	0.14
Disease characteristics				
Disease duration, years, median (IQR)	10 (6-16)	10 (5-16)	10 (6-15.5)	0.83
RF positive, n (%)	136 (80)	89 (77)	47 (84)	0.32
ACPA positive, n (%)	123 (72)	80 (70)	43 (77)	0.33
DAS28-CRP, mean (SD)	2.16 (0.68)	2.17 (0.65)	2.15 (0.76)	0.82
MBDA score, mean (SD)	33.7 (12.3)	33.8 (12.5)	33.4 (12.0)	0.82
Treatment characteristics				
Duration of current TNFi, mean (SD)	3.4 (2.4)	3.4 (2.4)	3.5 (2.2)	0.73
Etanercept, n (%)	111 (65)	74 (64)	37 (66)	0.83
Adalimumab, n (%)	60 (35)	41 (36)	19 (34)	0.83
Previous bDMARDs, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.79
Concomitant therapy, n (%)				
sDMARD	114 (67)	70 (61)	44 (79)	0.02
Methotrexate	93 (54)	55 (48)	38 (68)	0.01
Glucocorticoids	8 (5)	5 (4)	3 (5)	0.77
NSAIDs	96 (56)	64 (56)	32 (57)	0.85

RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; DAS28: 28 joint based disease activity score with C reactive protein; MBDA: multi-biomarker disease activity; bDMARD: biologic disease modifying anti rheumatic drug; sDMARD: synthetic DMARD; NSAIDs: Non-steroidal anti-inflammatory drug.

Table 2. Multi-biomarker disease activity scores and DAS28-CRP at baseline

18-Month outcome	MBDA	DAS28-CRP
Successfully stopped (N=22)	33.6 (13.1)	2.05 (0.62)
Successfully tapered (N=51)	34.4 (11.3)	2.08 (0.60)
No tapering possible (N=42)	33.3 (13.7)	2.34 (0.70)
Usual care (N=56)	33.4 (12.0)	2.15 (0.76)
Total (N=171)	33.7 (12.3)	2.16 (0.68)

Values given as mean (SD). MBDA: multi-biomarker disease activity.

Association of MBDA score with DAS28-CRP

Spearman correlation between MBDA score and DAS28-CRP at baseline demonstrated a significant but low ρ value (ρ=0.2, P=0.01) (Table 3). Correlations of subcomponents of DAS28-CRP with MBDA score at baseline were greatest for CRP (ρ=0.60, P<0.01) and lowest for tender joint count (ρ=0.05, P=0.49) (Table 3). Cross-classification of baseline MBDA score and baseline DAS28-CRP showed that most patients (81%) had low disease activity by DAS28-CRP, yet 65% had moderate or high MBDA scores (Table 4). Agreement by Cohen's κ with quadratic weighting was 0.02.

Table 3. Spearman's correlations of baseline multi-biomarker disease activity score vs. DAS28-CRP and its subcomponents

	Spearman's ρ	p-value
DAS28-CRP	0.20	0.01
TJC	-0.05	0.49
SJC	0.01	0.88
VAS-DA	0.05	0.50
CRP	0.60	<0.01

DAS28-CRP: 28-joint count disease activity score with C-reactive protein; TJC: tender joint count; SJC: swollen joint count; VAS-DA: visual analogue scale disease activity; MBDA: multi-biomarker disease activity.

Table 4. Cross-classification of DAS28-CRP and multi-biomarker disease activity score

	MBDA			
DAS28-CRP	**Low**	**Moderate**	**High**	**Total**
Low	48	66	24	138
Moderate	11	14	5	30
High	0	2	1	3
Total	59	82	30	171

Weighted (quadratic) Cohen's κ was 0.02. MBDA: multi-biomarker disease activity.

Predictive value of baseline MBDA score

Successful tapering and discontinuation

AUROC for predicting successful tapering vs. no tapering possible by baseline MBDA score was 0.53 (95% CI 0.41-0.66) (Table 5). AUROC for predicting successful discontinuation vs. no discontinuation possible by baseline MBDA score was 0.51 (95% CI 0.36-0.66) (Table 5; AUROC curves in Supplementary Figure 1a and 1b).

Table 5. Prediction analyses (Area Under Receiver Operating Characteristics curves) using baseline multi-biomarker disease activity score

	Tapering (N=115)	Usual care (N=56)	Total (N=171)
Tapering/discontinuation			
Successful tapering	0.53 (0.41-0.66)	-	-
Successful discontinuation	0.51 (0.36-0.66)	-	-
Flaring			
Flare	0.44 (0.32-0.57)	0.63 (0.46-0.80)	0.50 (0.41-0.59)
Major flare	0.35 (0.18-0.53)	0.72 (0.56-0.88)	0.46 (0.32-0.65)
Radiographic progression			
>0.5 SvdH points	0.49 (0.37-0.60)	0.67 (0.46-0.87)	0.53 (0.43-0.63)
>3 SvdH points	-	-	0.46 (0.25-0.68)
>5 SvdH points	-	-	0.68 (0.39-0.99)

AUROC (Area Under the Receiver Operating Characteristic Curves) values (95% CI). For radiographic progression analyses, N values: 111, 56 and 167. SvdH: Sharp-van der Heijde score.

Flare and major flare

AUROC for predicting any (i.e., first) flare by baseline MBDA score was 0.50 (95% CI 0.41-0.59) for both groups combined; 0.44 (95% CI 0.32-0.57) for the taper group and 0.63 (95% CI 0.46-0.80) for the usual care group (Table 5; Supplementary Figure 2a and 2b). AUROC for predicting major flare by baseline MBDA score was 0.46 (95% CI 0.32-0.65) for both groups combined; 0.35 (95% CI 0.18-0.53) for the taper group and 0.72 (95% CI 0.56-0.88) for the usual care group (Table 5; Supplementary Figure 2c and 2d). After removal of patients who were not having in low disease activity at baseline (DAS28-CRP>3.2), AUROC for any flare by baseline MBDA score was 0.52 (95% CI 0.43-0.61) for all patients combined: 0.40 (95% CI 0.27-0.53) for the taper group and 0.70 (95% CI 0.53-0.87) for the usual care group. For major flare, AUROC was 0.47 (95% CI 0.32-0.61) for all patients combined: 0.34 (95% CI 0.17-0.52) in the taper group and 0.79 (95% CI 0.64-0.95) in the usual care group. The time to flare is represented in Kaplan-Meier curves for the low, moderate or high MBDA categories in the taper and usual care groups, respectively (Supplementary Figures 3a and 3b). No association between MBDA category and flare was present in the taper group. In the usual care group, a trend toward an association of greater MBDA score with more frequent flares was observed.

Radiographic progression

AUROC for predicting radiographic progression of >0.5 SvdH point by baseline MBDA score was 0.53 (95% CI 0.43-0.63) for the taper and usual care groups combined; 0.49 (95% CI 0.37-0.60) for the taper group; 0.67 (95% CI 0.46-0.87) for the usual care group (Supplementary Figure 4a and 4b). AUROCs for predicting progression by SvdH cut-off values of 3 and 5 points in the total group were also non-significant (Table 5).

Cumulative probability plots of radiographic progression (i.e., change in SvdH from baseline to 18 months) for the low, moderate and high categories of baseline MBDA score demonstrated no association between MBDA category and progression rate in the taper group and a trend toward greater progression among patients with high MBDA score in the usual care group (Supplementary Figure 5).

5.1

Discussion

This is one of the first studies to investigate the MBDA score in patients with long-standing RA who tapered TNFi treatment. Our primary findings are that the MBDA score before the initiation of tapering was not predictive of successful tapering or stopping of TNFi treatment, occurrence of flare or major flare, or radiographic progression in the clinical context of DRESS, a study of long-standing RA patients tapering TNFi under tight control [14].

Our findings seem robust and valid, at least in this specific context. The design, determinant and outcome measurements, analyses and reporting used for this diagnostic prediction study, closely follow STARD recommendations [19]. Although this study was not a priori powered for these analyses, the sample sizes appear to be reasonable, as witnessed by sufficiently narrow confidence intervals. Finally, most of our analyses show similar results.

Some misclassification of successful dose tapering or discontinuation may be present in this study. Although we used a previously validated flare criterion in the study protocol [15], a proportion of patients could have been falsely classified as being unable to taper or stop if, for example, their continuation of TNFi treatment was due to fear of flaring (by patient or rheumatologist) rather than actual flare symptoms. This effect could have caused a bias towards lower correlation measures, but it seems unlikely that it would have caused the null results that were found. It is possible that treatment administered for flares altered the relationship between baseline MBDA score and the subsequent declaration of major flares, potentially explaining that negative finding. However, the relationship between simple flares and MBDA score should not have been comparably affected.

A borderline positive predictive value of baseline MBDA score for major flare was found in the entire usual care group and for flare and major flare in usual care patients who had low disease activity at baseline. These results should be interpreted cautiously as they may be false positive findings due to multiple testing. In addition, the association with major flare in the tapering group was nearly significant in the opposite direction (higher MDBA score associated with less flare). Review of medication use (sDMARDs and steroids) during the trial does not indicate that patients in the taper group were treated more aggressively in anticipation of flare, which if true, may have caused flares to be less prevalent and less severe in that arm [14]. Also, in this scenario we may have found significant AUROCs for flares, which were untreated, whereas we found only a non-significant trend in the usual care group.

The capability of the MDBA score to predict outcomes after reduction of RA treatment has been evaluated in two other studies, RETRO and POET [20,21]. Both studies differed from DRESS in several ways, and both reported the MBDA score to be a significant predictor of outcomes.

Rech et al. described the predictive value of the MBDA score for relapse in RETRO, a 3-arm, 12-month RCT of dose tapering and discontinuation of bDMARDs and sDMARDs for RA patients in sustained DAS28 remission [20]. MBDA score and ACPA were each predictive for relapse vs. remaining in remission, with improved predictive value when they were used together. Interpretation of this result needs to consider that all RA medications, including bDMARDs, sDMARDs and low dose steroids, were tapered in RETRO, with or without subsequent discontinuation. Moreover, only one-third of patients in the treatment reduction arms were using a bDMARD, which included TNFi and tocilizumab. Thus, it is unclear which tapered medications were responsible for the predictive ability of MBDA score or ACPA in that cohort[20]. Relapse was more frequent in RETRO than major flares were in DRESS, possibly due to the different reduction strategies and definitions for loss of response. In DRESS, neither MBDA score nor ACPA was predictive of flares following TNFi tapering [14].

A subanalysis of POET showed that the MBDA score was a predictor for flare after TNFi discontinuation during 12 months follow-up [21]. POET enrolled patients with long-standing RA, like DRESS, and with a requirement of stable low disease activity by DAS28 while receiving adalimumab or etanercept. Only patients who were randomized to discontinuation were included in the subanalyses. The sample size in the analysis of MBDA score in POET was large (N=439). The primary clinical objective of POET used a DAS28-based flare criterion that was not included in the analyses of prediction by MBDA score [21,22]. The four flare definitions that were used for the prediction analyses were based on physician/patient judgment or decision [21]. The occurrence of a flare in POET increased from approximately 60% to 80% between patients with low vs. high baseline MBDA score, suggesting that, in that context, the MBDA score was most applicable for predicting who was at greatest risk of flare, and not who was at low risk. Results of RETRO and POET are intriguing but comparing them with DRESS is difficult due to differences in design and analyses.

Our finding that radiographic progression was not associated with baseline MBDA score in DRESS disagrees with five studies in four cohorts of patients, with established RA [11,12,23] or early RA [13,24]. The different results might be due to the low frequency and severity of radiographic progression in our study, with only a small difference in favor of the usual care group. It might reflect the strict tight control that was applied to patients who were already in low disease activity or remission. Moreover, several variables that may have driven radiographic progression in DRESS – tapering with associated flaring, temporary increases in disease activity, and reduced TNFi use – occurred after baseline and may have disconnected radiographic progression from the baseline MBDA score. MBDA score was also reported to not be associated with radiographic progression among patients treated with abatacept or adalimumab in the AMPLE study [25]. This conclusion was based on the analysis that presented the distribution of radiographic non-progressors across the low, moderate and high MBDA categories, rather than the frequency of radiographic non-progressors within MBDA categories. A subsequent re-analysis of the same data from AMPLE used, instead, an approach similar that of prior MBDA analyses and demonstrated that the MBDA score was positively associated with radiographic progression in AMPLE, although numbers of patients with progression were low [26]. Additional data from AMPLE supported the findings of this re-analysis [27]. This positive relationship between MBDA score and radiographic progression in AMPLE is thus consistent with the results of other studies which, unlike DRESS, did not employ a tapering strategy [11–13,23,24].

In summary, the baseline MBDA score was not found to be a predictor of flare-related outcomes for patients tapering TNFi in the clinical context of DRESS – a study of disease activity-guided TNFi tapering in patients with long-standing RA under tight control. It is conceivable that in different contexts, for example in early RA patients, patients with higher levels of disease activity, or circumstances with less than optimal tight control, the MBDA score may have predictive value for relevant clinical outcomes. Confirmatory research of these findings is warranted.

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5.1

data. The manuscript was written by CB under the supervision of AvdM and AdB. All authors were involved in writing, revision and final approval of the manuscript. CB is study guarantor.
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Ethical approval

This study was approved by the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, NL37704.091.11).

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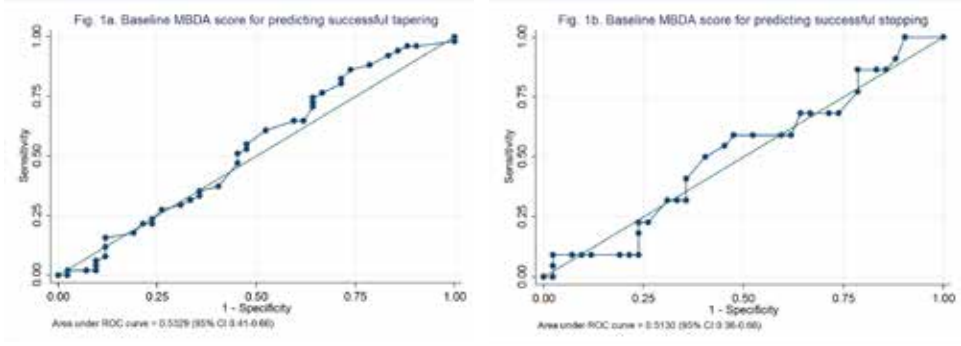
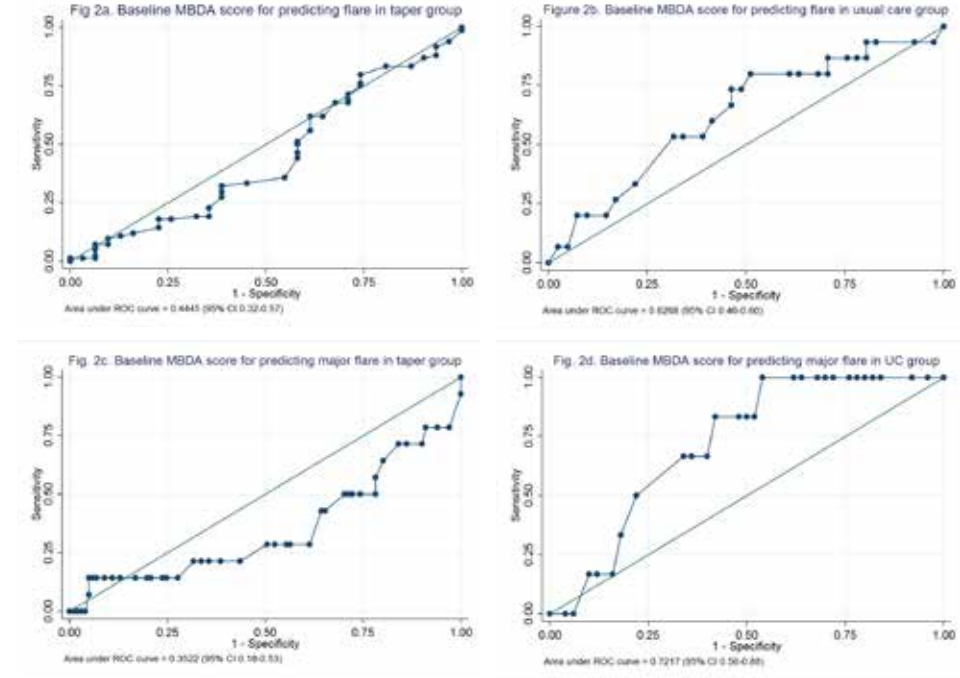
SUPPLEMENTARY DATA

Supplementary Figure S1. Baseline multi-biomarker disease activity score predicting successful tapering (A) or stopping (B)



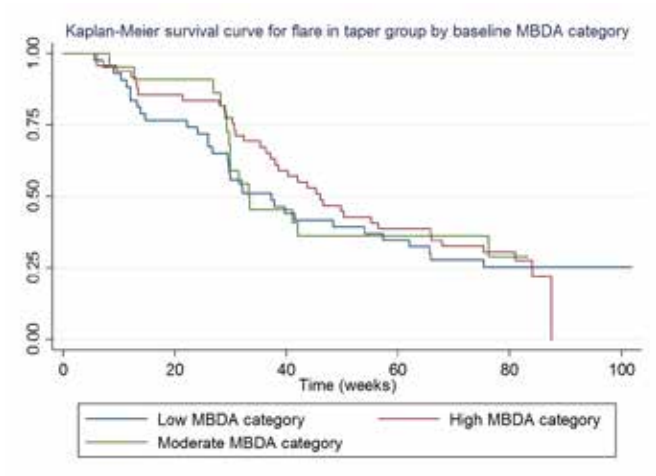
Prediction analyses using receiver operating curves. Successful tapering: n=51; successful stopping: n=26.

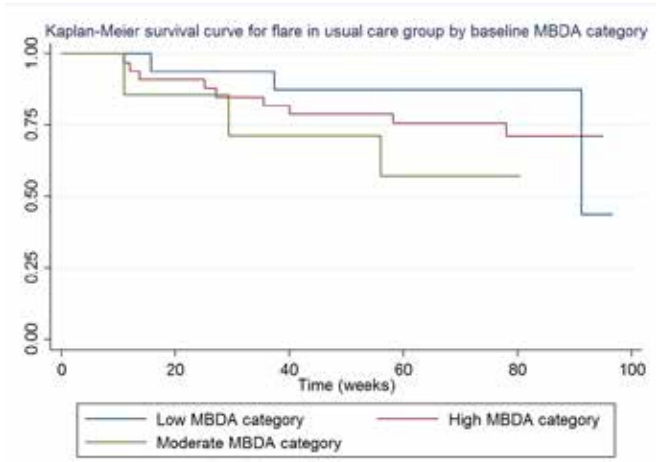
Supplementary Figure S2. Baseline multi-biomarker disease activity score predicting flare and major flare in the taper and usual care group



Prediction of flare in the taper (A) and usual care (B) groups; prediction analyses using receiver operating curves. Flare in the taper group: n=84; flare in the usual care group: n=15. Prediction of major flare in the taper (C) and usual care (D) groups; prediction analyses using receiver operating curves. Major flare in the taper group: n=14; major flare in the usual care group: n=6.

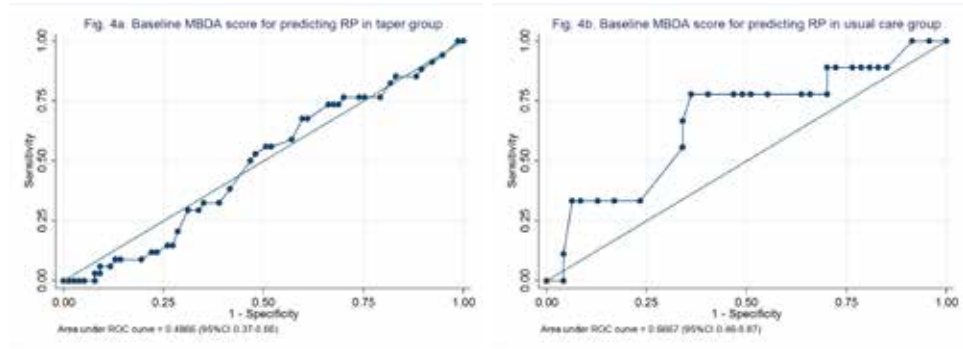
Supplementary Figure S3. Kaplan-Meier curves for flare by baseline multi-biomarker disease activity category





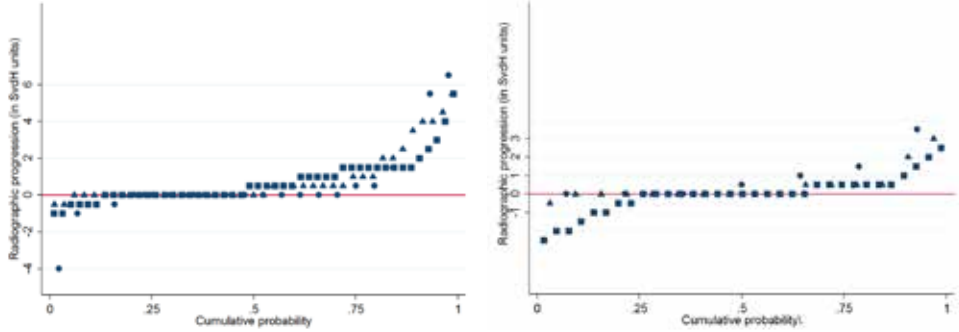
A) Taper group (n=115): low MBDA score (n=43); moderate MBDA score (n=49); high MBDA score (n=23). B) Usual care group (n=56): low MBDA score (n=16); moderate MBDA score (n=33); high MBDA score (n=7).

Supplementary Figure S4. Baseline multi-biomarker disease activity score predicting radiographic progression



Prediction analyses using receiver operating curves. A) Baseline MBDA score for predicting RP in taper group. B) Baseline MBDA score for predicting RP in usual care group. Occurrence of radiographic progression in the taper group: n=34; usual care group: n=9.

Supplementary Figure S5. Cumulative probability plots for radiographic progression by multi-biomarker disease activity category



A) Taper group (n=111): low MBDA score, n=41; moderate MBDA score, n=48; high MBDA score, n=22. B) Usual care group (n=56): low MBDA score, n=16; moderate MBDA score, n=33; high MBDA score, n=7. Triangles: low MBDA score; Squares: moderate MBDA score; Circles: high MBDA score. SvdH: Sharp-van der Heijde score; MBDA: multi-biomarker disease activity.

5.1

Chapter 5.2

Prediction of successful dose reduction or discontinuation of adalimumab, etanercept or infliximab in rheumatoid arthritis patients using serum drug levels and antidrug antibody measurement

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Abstract

Background
To evaluate if TNF inhibitor serum drug levels (DL) or anti-drug antibodies (ADAb) can predict successful dose reduction (in patients with high DL) or discontinuation (in patients with no/low DL or ADAb) in rheumatoid arthritis (RA) patients.

Research design and methods
RA patients that were using adalimumab (n=42), etanercept (n=76) or infliximab (n=51) and were doing well, were tapered until discontinuation or flare (1-1.5 year follow up). Random timed DL for adalimumab and etanercept and trough DL for infliximab were measured before dose reduction: Receiver-Operator-Curves (ROC) analyses with optimal cut-off DL were determined.

Results
No predictive value of adalimumab and infliximab DL for all outcomes were found, except for an inverse association of lower etanercept DL and higher chance for successful dose reduction (Area Under the Curve (AUC) 0.36, 95%CI 0.23-0.49; cut-off <2.6 mg/l). In sub analyses, higher adalimumab trough DL predicted successful dose reduction (AUC 0.86, 0.58-1.00; cut-off >7.8). ADAb were infrequent and not predictive of successful discontinuation.

Conclusion
No predictive value of baseline adalimumab, etanercept and infliximab DL or ADAb for successful dose reduction or discontinuation in RA was found in this context, with the possible exception of high adalimumab trough levels for successful dose reduction.

Introduction

Tumour necrosis factor inhibitors (TNFi) have proven to be effective in clinical, functional and radiographic outcomes in patients with rheumatoid arthritis (RA)[1]. However, TNFi are costly and are associated with (dose-dependent) side effects, like infections and melanoma[2-4]. Optimal use of these drugs is therefore warranted, by, amongst others, using the lowest effective dose in the individual patient, and discontinuing treatment when this is no longer necessary.

A number of studies in patients who achieve persistent low disease activity demonstrated that dose reduction and discontinuation is possible in a relevant proportion of patients without increase in disease activity[5]. However, disease activity guided dose reduction in the subset of patients already using the optimal dose, will lead to (temporary) flaring of disease activity. Although, fortunately, dose escalation or restart of the drug is effective in the majority of patients[5], and short lived flares do not seem to compromise quality of life, functioning or radiological outcome[6], they can still present a burden for patients.

Prediction of successful dose reduction or discontinuation in addition to a disease activity guided type of dose reduction could have two advantages: 1) in patients in whom TNFi can only partially be dose reduced or in whom dose reduction is not possible at all, the flares caused by the dose reduction attempt can be prevented and 2) when successful discontinuation can be predicted, no dose reduction phase is necessary, thus saving time and medication. So far, no evident biomarkers that are able to predict successful dose reduction or discontinuation have been identified[7].

Possible predictors for successful dose reduction or discontinuation could be TNFi serum drug levels (DL) and anti-drug antibodies (ADAb). Clinical scenarios have been proposed in which measurement of TNFi DL or ADAb is suggested to be valuable in patients doing well (with low disease activity)[8-10]. These scenarios follow classic pharmacokinetic rules, based on the concept of a therapeutic window with an upper and lower boundary, and they share two central hypotheses: 1) a patient with low disease activity and no or low DL and/or ADAb has a higher chance of successful discontinuation of the TNFi, as the dose is below the lower boundary of the therapeutic window and a clinical effect might not be expected and 2) a patient with low disease activity and a high DL has a higher chance of successful dose reduction, as the same clinical effect is to be expected with a lower dose (that is still within the therapeutic window). Although these hypothesis seem rational, studies testing these hypotheses with the appropriate design[11] are scarce.

Therefore, the aim of this study was to investigate whether serum TNFi DL and/or presence of ADAb can predict successful dose reduction or withdrawal of adalimumab, etanercept or infliximab in RA patients with stable low disease activity. Our study has nine separate null hypotheses, three for each TNFi. These are, that there is 1) no positive association between high drug levels with successful dose reduction, 2) no positive association between low drug levels and successful stopping, and 3) no positive association between the presence of anti-drug antibodies and successful stopping. In addition to testing these hypotheses, validation analyses of previously proposed cut-off levels for high or low adalimumab, etanercept and infliximab drug levels will be done by calculating sensitivity and specificity.

Patients and methods

Study population and design

RA patients from 2 different studies were included for analyses: 1) patients included in the intervention arm of an open randomised clinical trial investigating non-inferiority of a dose reduction strategy of adalimumab or etanercept compared to usual care, and 2) patients from an observational cohort study on dose reduction and discontinuation of infliximab[6,12]. The study on adalimumab/etanercept has been approved by the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, NL37704.091.11). The study on infliximab was an observational cohort study and this study did not require approval of an ethical committee according to Dutch legislation. Data on prediction of successful dose reduction or discontinuation by using baseline adalimumab or etanercept has been described shortly in a previously published letter[13]. Analyses done in this letter have been extended with sensitivity analyses. Furthermore, data on infliximab drug levels and antidrug antibodies have not been published as full text article previously.

In both studies RA patients (either 2010 ACR RA and/or 1987 RA criteria and/or clinical diagnosis of the treating rheumatologist) using adalimumab, etanercept or infliximab in any stable dose and with a low disease activity (judged by the rheumatologist) for at least 6 months were included. Patients were treated according to the tight control principle. Visits were planned every 3 months and patients were encouraged to contact the outpatient clinic if they experienced deterioration of disease activity. Follow-up was 18 months for patients in whom dose reduction of adalimumab or etanercept was attempted and 12 months for patients in whom infliximab dose reduction was attempted.

For patients dose reduction adalimumab or etanercept, the dose reduction strategy consisted of stepwise increasing the interval between injections every three months. For adalimumab these steps were: 1) 40 mg every 21 days, 2) 40 mg every 28 days, 3) discontinuation. For etanercept these steps were: 1) 50 mg every 10 days, 2) 50 mg every 14 days, 3) discontinuation. For patients dose reduction infliximab, the dose was reduced with 25% of the baseline dose (3 mg/kg) every 8 to 12 weeks until discontinuation.

In case of flare, the last effective interval was reinstated. If the flare persisted, TNFi was increased until the shortest registered interval or the last effective dose. If the flare persisted thereafter, treatment was switched. A flare was defined using a DAS28 based flare criterion (14): a DAS28 increase of >1.2 or a DAS28 increase of >0.6 and current DAS28 ≥3.2. In the infliximab cohort DAS28 was used, whereas in the DRESS study, DAS28-CRP was used with the same cut-off levels for flare. In the DRESS study, re-escalation was deemed necessary if the flare criterion was met for ≥4 weeks. In the cohort study of patients using infliximab, the flare criterion was met if it lasted ≥2 weeks.

At study end (month 18 in the DRESS study and month 12 in the infliximab cohort study), patients were categorised as 1) successful dose reduction (lower dose or longer interval than at baseline with concurrent low disease activity), 2) successful discontinuation (complete withdrawal of the bDMARD with concurrent low disease activity), 3) no dose reduction possible (back at dose/ interval used at baseline or higher dose/shorter interval than used at baseline or switched to another bDMARD).

Assays

Serum samples were collected at baseline (before initiation of dose reduction). For pragmatic reasons, for adalimumab and etanercept, serum samples were collected at a regular outpatient clinic visit, thus unrelated to time of injection. The time of the previous and next adalimumab or etanercept injection was noted. For infliximab, serum samples were collected just before administration of the next infliximab dose, thus timed at trough level. Serum adalimumab, etanercept and infliximab levels were measured batch wise, after the study was completed and blinded for individual patient outcome, using enzyme-linked immunosorbent assay (ELISA) based on their ability to bind TNF[15,16].

Adalimumab trough levels have been proposed to be therapeutically low when <5 mg/l and high when >8 mg/l [17,18*], for etanercept previously published thresholds were low when <1.8 mg/l and high when >4.6 mg/l [19*], and for infliximab, thresholds were low when <1.0 mg/l and high when >5.0 mg/l [20-22], all on a group level.

Anti-adalimumab and anti-infliximab antibodies were assessed using a validated antigen-binding test (Radio Immuno Assay (RIA)). Anti-adalimumab antibodies were considered positive based on the lower limit of detection if both the value was >12 arbitrary units/ml and the adalimumab level was <5mg/l [16]. Anti-infliximab antibodies were considered positive if both the value was >12 arbitrary units/ml and trough level was <1.0 mg/l [21]. Anti-etanercept antibodies were assessed using different assays; RIA, bridging ELISA and IgG4-ABT[15].

Statistical analyses

Associations were analysed using Receiver Operator Curve (ROC) analyses and calculation of the point estimates of the area under the curve (AUC) and surrounding confidence interval, to test whether the lower limit of the confidence interval was above 0.5.

Sample size calculation showed that, with a null hypothesis of a ROC AUC of 0.5, an expected AUC of 0.75, an event rate of 20% (being able to stop) to 40% (being able to dose reduce), a total of 65 to 43 patients per drug (adalimumab, etanercept or infliximab) respectively were needed to be able to reject a null hypothesis with a power (1-beta) of 0.8 and alpha of 0.05.

Descriptive statistics were used for demographic or clinical data. Percentages of patients were calculated for three different outcomes: successfully stopped, successfully dose reduced (lower dose/higher interval than baseline) or no dose reduction possible. Mean drug levels and proportions of patients with anti-drug antibodies were calculated and differences in mean drug levels between groups were tested using a t-test. For the primary analysis, ROC with optimal cut-off levels (using Youden) were created for adalimumab, etanercept and infliximab levels, and for the presence of anti-drug antibodies, versus the outcomes successful discontinuation and successful dose reduction separately, compared to the 'no dose reduction possible' group. Additionally, validation analyses were done by calculating sensitivity and specificity of previously proposed cut-off levels. Because adalimumab and etanercept sampling was done at random time in relation to injection instead of trough level timing, exploratory sub analyses were done for three groups of patients with approximately peak sampling (adalimumab day 1-4 and etanercept day 1-2 after last injection), trough sampling (adalimumab 11-14 days and etanercept 6-7 days after last injection) and intermediate timed sampling. No correction for multiple testing was applied.

Results

Patient characteristics and baseline (anti) drug levels

For details on patients' disposition of both studies, we refer to Supplement 1. Baseline serum samples and outcome were available for 42 patients using adalimumab, 76 using etanercept and 51 patients using infliximab (Table 1). 3 patients using etanercept were excluded because of missing serum sample (n=2) and being lost to follow-up after 3 months (n=1). The numbers and percentages of patients that could successfully reduce the dose or discontinue or were not able to reduce the dose are depicted in table 2. Mean drug levels and anti-drug antibodies were not significantly different between the three outcome subgroups (Table 2). Anti-adalimumab antibodies (low titres, 15 to 46 U/ml) were detected in 4 patients (10%), 2 patients used methotrexate co-medication, the other 2 patients used adalimumab monotherapy. No anti-etanercept antibodies were detected. Anti-infliximab antibodies were detected in 8 patients (16%) of whom 7 were treated with concomitant DMARDs (methotrexate, leflunomide and azathioprine).

Table 1. Baseline patient characteristics

bDMARD	ADM (n=42)	ETA (n=76)	IFX (n=51)
Age, years (SD)	61 (8.2)	58 (10.7)	59 (11.2)
Female, n (%)	27 (64)	46 (61)	29 (57)
Current smoking, n (%)	13 (31)	14 (18)	8 (16)
BMI (SD)	27 (5.0)	27 (4.8)	26 (3.4)
Diagnosis according to 2010 and/or 1987 ACR criteria, n (%)	42 (100)	70 (93)	51 (100)
Disease duration, years median [p25-p75]	7.5 [5-15]	13 [10-21]	12 [9-18]
RF positive, n (%)	32 (76)	60 (79)	42 (82)
ACPA positive, n (%)	32 (76)	51 (67)	37 (73)
DAS28-CRP (SD)	2.2 (0.6)	2.2 (0.7)	-
DAS28-ESR (SD)	2.6 (0.8)	2.4 (0.7)	2.5 (0.7)
Duration of current TNFi therapy, years (SD)	4.5 (2.2)	2.9 (2.5)	5.6 (2.6)
Previous sDMARDs, median [p25-p75]	2 [1-3]	2 [1-3]	3 [2-3]
Previous TNFi, median [p25-p75]	1 [0-1]	0 [0-1]	5 (10)
Concomitant therapy			
sDMARD, n (%)	27 (64)	45 (59)	41 (80)
MTX, n (%)	23 (55)	34 (45)	35 (68)
glucocorticoid, n(%)	2 (5)	3 (4)	2 (4)
NSAID, n (%)	23 (55)	42 (55)	27 (53)

bDMARD=biologic Disease Modifying AntiRheumatic Drug; ADM= adalimumab; ETA= etanercept; IFX= infliximab; BMI= Body Mass Index; RF= rheumatoid factor; ACPA= anti-Citrullinated Peptide Antibodies; DAS28= 28 joints disease activity score; CRP= C reactive protein; TNFi= Tumor Necrosis Factor inhibitor; sDMARD=synthetic Disease Modifying AntiRheumatic Drug; MTX= Methotrexate; NSAID= Non-Steroidal Anti Inflammatory Drug

Table 2. Mean or median drug levels and antidrug antibodies at baseline

A: adalimumab (n=42)

Outcome at 18 months	Mean drug level at baseline mg/l (SD)		Anti-drug antibodies (%)
Successfully discontinued, n=11 (26%, 95% CI 14 to 42%)	8.5 (2.8)		0
Successfully dose reduced, n=15 (36%, 95% CI 22 to 52%)	8.1 (5.2)	ns	1 (7)
No dose reduction possible, n=16 (38%, 95% CI 24 to 54%)	6.8 (4.1)		3 (19)

B: etanercept (n=76)

Outcome at 18 months	Mean drug level at baseline mg/l (SD)		Anti-drug antibodies (%)
Successfully discontinued, n=11 (15%, 95% CI 7 to 24%)	2.7 (1.3)		0
Successfully dose reduced, n=37 (49%, 95% CI 37 to 60%)	2.0 (0.9)	ns	0
No dose reduction possible, n=28 (37%, 95% CI 26 to 49%)	2.4 (1.0)		0

C: Infliximab (n=51)

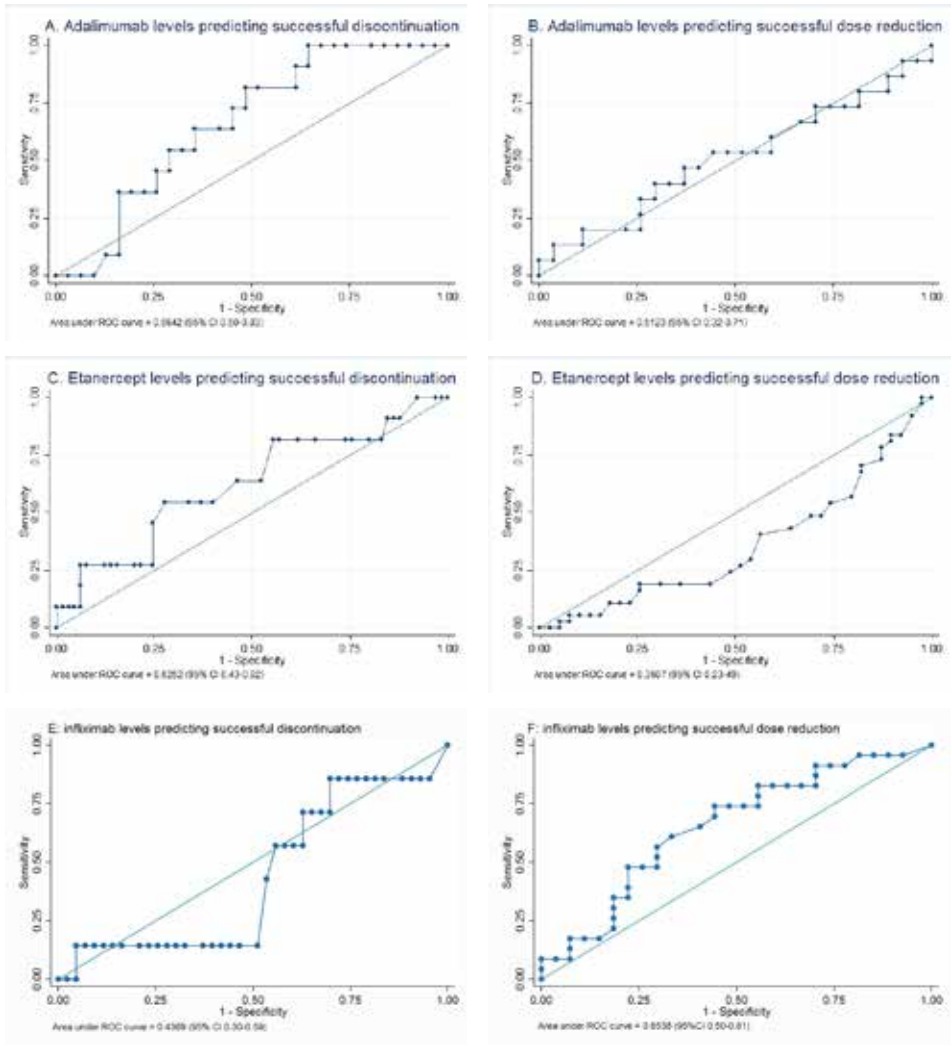
Outcome at 12 months	Median drug level at baseline mg/l (IQR)		Anti-drug antibodies (%)
Successfully discontinued (n=8) (16%, 95% CI 7 to 29%)	1.0 (IQR 0.3-1.1)		1 (12.5)
Successfully dose reduced (n=23) (45%, 95% CI 31 to 60%)	1.7 (IQR 0.54-5.1)	ns	1 (4)
No dose reduction possible (n=20) (39%, 95% CI 26 to 54%)	0.55 (IQR 0.03-2.35)		6 (30)

SD=standard deviation; IQR=interquartile range; ns= not statistically significant

Primary analysis

ROC analyses showed no significant predictive value of adalimumab, etanercept or infliximab serum levels for successful dose reduction or discontinuation (Figure 1), except for a significant but small -inverse- association between lower etanercept levels and higher chance for successful dose reduction (AUC 0.36, 95% CI 0.23-0.49; optimal cut point <2.6 mg/l; sensitivity 81%, specificity 44%). Presence of anti-adalimumab or anti-infliximab antibodies was not predictive for successful discontinuation.

Figure 1. Receiver Operator Curves (ROC)



Exploratory sub analyses

Sensitivity and specificity of high, intermediate and low serum drug levels according to the previously published cut-off values of low, intermediate and high level for successful dose reduction, discontinuation or no dose reduction possible are depicted in table 3.

Table 3. Sensitivity and specificity for previously proposed high, low and intermediate drug level cut-off values for the outcomes successful dose reduction, discontinuation or no dose reduction possible

TNFi	Outcomes	Sensitivity (95%CI)	Specificity (95%CI)
Adalimumab level			
High (>8.0 mg/l)	Successful dose reduction	40% (16-68%)	63% (42-81%)
Low (<5.0 mg/l)	Successful discontinuation	0% (0-7%)	68% (49-83%)
Intermediate (5.0-8.0 mg/l)	No dose reduction possible	38% (15-65%)	62% (41-80%)
Etanercept level			
High (>4.6 mg/l)	Successful dose reduction	0% (0-4%)	95% (83-99%)
Low (<1.8 mg/l)	Successful discontinuation	18% (2-52%)	62% (48-93%)
Intermediate (1.8-4.6 mg/l)	No dose reduction possible	68% (48-84%)	42% (28-57%)
Infliximab level			
High (>5.0 mg/l)	Successful dose reduction	26% (10-48%)	82% (63-94%)
Low (<1.0 mg/l)	Successful discontinuation	50% (16-84%)	56% (40-71%)
Intermediate (1.0-5.0 mg/l)	No dose reduction possible	20% (6-44%)	58% (39-75%)

Mean serum drug levels for the different serum sampling times show a trend to lower levels with increasing time after injection, although the differences are small and mostly non-significant (Table 4).

Table 4. Mean serum levels for different sampling times

A: adalimumab n=42

Sampling time	Mean drug level at baseline mg/l (SD)	
Peak (n=11)	8.5 (5.6)	
Intermediate (n=22)	7.7 (4.2)	ns
Trough (n=9)	6.7 (2.0)	

B: etanercept n=76

Sampling time	Mean drug level at baseline mg/l (SD)		
Peak (n=25)	2.4 (1.2)	ns	
Intermediate (n=28)	2.5 (1.0)	-	-
Trough (n=23)	1.7 (0.6)		

SD=standard deviation; ns= not statistically significant
*p<0.05

A sensitivity analysis showed that for intermediate timed serum etanercept level, low levels were associated with a higher chance of successful dose reduction (AUC 0.28 95% CI 0.08-0.47) with an optimal cut point <2.5 mg/l and sensitivity 76% and specificity 67%. For adalimumab, high trough timed levels were associated with successful dose reduction (AUC 0.86, 95% CI 0.58-1.00), with trough levels >7.8 mg/l showing a sensitivity of 100% and a specificity of 86%. None of the patients had adalimumab trough levels ≥ 12 mg/l. All other prediction analyses (peak and trough for etanercept and intermediate and peak for adalimumab) showed non-significant results for successful dose reduction or discontinuation.

Discussion

We could not reject any of our null hypotheses with regard to the predictive value of (anti)drug levels of adalimumab, etanercept or infliximab for successful dose reduction or stopping of TNFi treatment in RA patients doing well. In contrast to the previously mentioned hypothesis, we did find a significant -inverse- association between lower etanercept levels and higher chance for successful dose reduction.
Our results are not directly conflicting with the established body of evidence, as other studies that test the hypotheses on which previously proposed treatment algorithms rely, using the appropriate design, are scarce. The most comparable data are the recently described analyses from the STRASS study[23], a randomised controlled trial on adalimumab or etanercept dose

reduction until discontinuation. In this paper the predictive value of baseline adalimumab or etanercept level and anti-drug antibodies for successful dose reduction or discontinuation in the STRASS study was assessed, and no predictive value could be proven for (anti-) drug level. Another study by Chen et al. did show that successful adalimumab dose halving was nearly perfectly predicted by baseline adalimumab trough levels. However, the extremely high AUROC curves led to the results being disputed [24,25]. Of note, for prediction of response after treatment start or dose escalation, two studies (prediction of response after golimumab dose escalation by means of golimumab trough levels in ankylosing spondylitis patients, and prediction of response after start of infliximab by means of infliximab trough levels in RA) could also not confirm a strong predictive value [26,27].
Seemingly conflicting results emerged from a number of cross-sectional or non-interventional studies, that did find (low to moderate) positive correlations between TNFi serum trough levels and response on a group level [8,18,18,19,28,29], although for etanercept, the association between drug level and response is unclear [30-32]. A possible explanation for this could be that, although dose-response curves have been found on a group level, concentration-response curves show high inter-individual variation in effective serum drug levels [16]. This means that the same serum drug level can be supra-therapeutical for one patient, but too low for another. Secondly, it has been suggested that the inflammation process itself may influence pharmacokinetics of TNFi, implying that for patients with higher disease activity, higher target levels are required [33,34]. Thus, it remains to be debated if weak associations found on a group level, can be translated to strong predictive test characteristics in an individual patient.
An important design choice in our study was that serum sampling was performed unrelated to timing of the next injection (random timed) for adalimumab and etanercept. This was done as trough sampling may be difficult to establish, since trough level sampling may require an extra visit when it does not coincide with a regular 3- or 6-monthly outpatient clinic visit. In most – though not all - studies, trough level sampling is opted for. This is based on the assumption that dose reduction is possible if trough levels are (much) higher than the minimum inhibitory concentration (MIC) of a drug, and that discontinuation is possible for trough levels lower than MIC. However, the difference between peak and trough categories for all three bDMARDs tested in these patients was small, which is consistent with previously described low peak and trough levels (peak-to-trough ratios) for subcutaneous TNFi [35]. Furthermore, for infliximab we did measure trough levels and both these analyses as well as additional sub analyses for timing relative to the following injection did not yield different results.
The results of the exploratory sub analyses are most likely false positive findings. An inverse association between (intermediate timed) etanercept serum levels and successful dose reduction (low intermediate timed serum etanercept level with a higher chance of successful dose reduction) was found, as well as a (positive) association between high adalimumab trough levels and successful dose reduction. This would suggest a predictive value of adalimumab trough levels above 7.8 mg/l, but this finding should be interpreted with caution, as previously found cut-offs for supra-therapeutical adalimumab trough levels ranged from 8 mg/l to 12 mg/l [10,17]. However, more importantly, these results are contradictive (and for etanercept counterintuitive) and most probably caused by multiple testing.
A notable finding was the low percentage of patients with anti-adalimumab and anti-infliximab antibodies (10% and 16%) compared to other studies (17-30% RIA measured anti-adalimumab antibodies and 13-50% RIA measured ant-infliximab antibodies) in RA patients[8]. This difference might be explained by the fact that included patients were having long-standing RA and had been treated with tight control for an extensive period of time prior to

participation in this study. Patients not responding (which could theoretically be caused by anti-drug antibodies) would have been switched to another bDMARD already. This patient selection does not invalidate our findings, however, as it is compatible with current state of art RA care and therefore this represents a relevant study population, although these findings may not be generalisable to early RA patients Nevertheless, this means that even if we would have found an association between anti-drug antibodies and successful discontinuation in our study, the low prevalence of anti-drug antibodies in this population, would lead to a high number needed to diagnose (NND). However, in contrast to previously mentioned hypotheses, in our study, we observed the numerical lowest prevalence of ADAb in patients that were able to discontinue their TNFi instead of the highest.
All in all, the hypothesis that either random timed or trough serum TNFi levels can be used for prediction of successful dose reduction or discontinuation and anti-drug antibodies for successful discontinuation in RA patients doing well on adalimumab, etanercept or infliximab could not be confirmed in this setting.

Conclusions

This study showed that serum TNFi drug levels or anti-drug antibodies cannot predict successful dose reduction or discontinuation of adalimumab, etanercept or infliximab in rheumatoid arthritis patients with stable low disease activity. Since measurement of serum TNFi drug levels or anti-drug antibodies was not useful in rheumatoid arthritis patients in whom adalimumab, etanercept or infliximab were tapered, these tests should not be used in this clinical setting.

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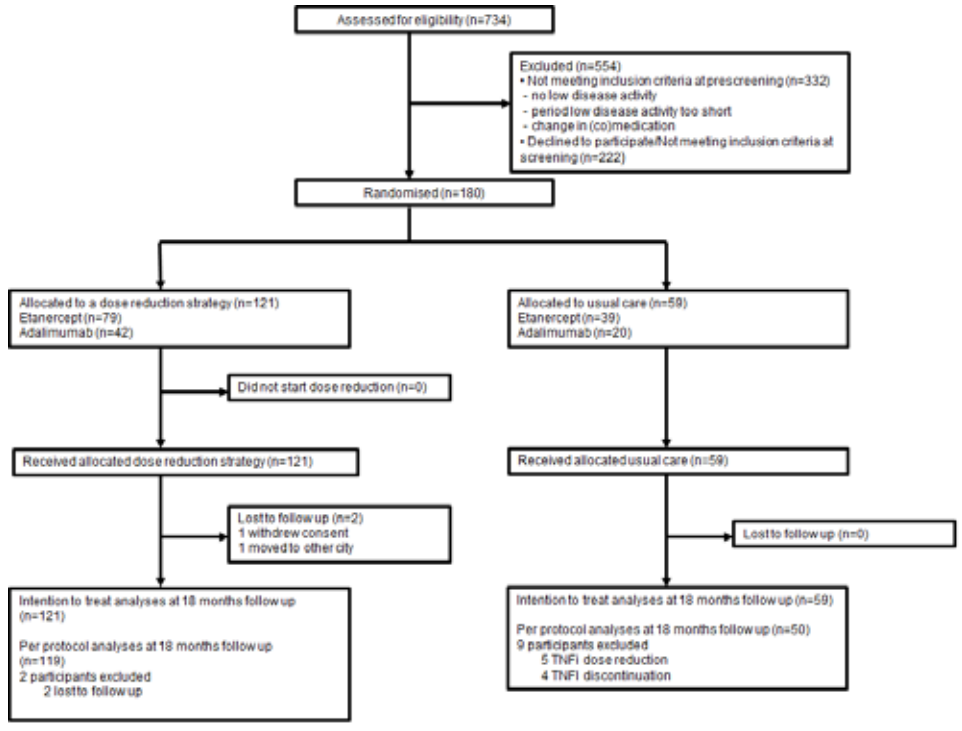
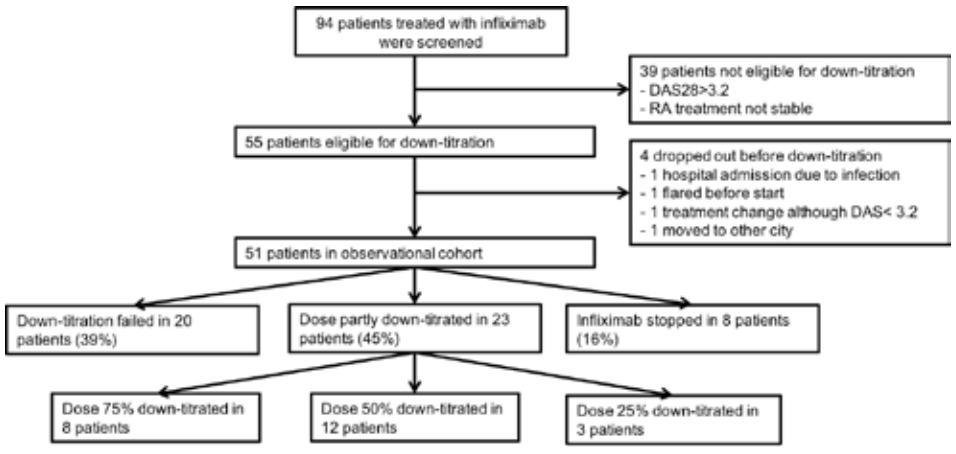
SUPPLEMENT 1

Supplementary figure 1. Flow chart with patients' disposition for **A.** adalimumab or etanercept and **B.** infliximab.

1A.



1B.


94 patients treated with infliximab were screened
39 patients not eligible for down-titration
- DAS28>3.2
- RA treatment not stable
55 patients eligible for down-titration
4 dropped out before down-titration
- 1 hospital admission due to infection
- 1 flared before start
- 1 treatment change although DAS< 3.2
- 1 moved to other city
51 patients in observational cohort
Down-titration failed in 20 patients (39%)
Dose partly down-titrated in 23 patients (45%)
Infliximab stopped in 8 patients (16%)
Dose 75% down-titrated in 8 patients
Dose 50% down-titrated in 12 patients
Dose 25% down-titrated in 3 patients

Chapter 6

Summary and general discussion

Introduction

Rheumatoid arthritis (RA) treatment outcomes have improved in the last decades by the introduction of drugs like biologic Disease Modifying Anti-Rheumatic Drugs (bDMARDs) and targeted synthetic Disease Modifying Anti-Rheumatic Drugs (tsDMARDs), as well as new treatment strategies including 'hit hard, hit early', 'tight control' and 'treat-to-target'. These developments have led to more patients achieving low disease activity or remission. Rheumatoid arthritis is considered a chronic disease, but due to improved outcomes the question has been raised whether patients could lower the dose of their drugs or even (temporarily) stop them. Tapering may be motivated by patient preferences, to reduce adverse events and to lower costs.[1-3] Previous studies have already shown that tapering of bDMARDs in RA patients with stable low disease activity or remission is feasible and safe,[4,5] at least in the short term, and this has lead to the addition of disease activity guided tapering as treatment recommendation in the international RA treatment guidelines.[6] This thesis further increases the existing body of knowledge on dose optimisation of bDMARDs in patients with RA.

Main findings

Dose optimisation of tumor necrosis factor inhibitors (TNFi) has been investigated in a number of studies. In a previous review, immediate discontinuation has shown to be inferior to full dose continuation.[4] It was hypothesized that disease activity guided tapering until discontinuation may be non-inferior to full dose continuation. This was investigated in the DRESS study: a pragmatic randomised open-label non-inferiority trial comparing dose tapering of adalimumab and etanercept with full dose continuation in RA patients with stable low disease activity. This study shows that tapering is non-inferior to full dose continuation with regard to risk for major flare, although short-lived flare and minimal radiographic progression were more frequent in the tapering group.[7]

Chapter 2.1, investigates the long-term effects of the disease activity guided dose optimisation strategy used in the DRESS study by performing a long-term extension study. In the intervention phase (months 0-18), patients were randomised to either tapering or usual care. In the tapering group, the intervention consisted of stepwise tapering of adalimumab or etanercept until discontinuation or until flare. In the usual care group, patients continued with full dose adalimumab or etanercept under tight control. In the extension phase (months 18-36) treatment strategies in both groups converged to the same treatment strategy: treatment choices were left to the discretion of the treating rheumatologist with dose optimisation being allowed in both groups after low disease activity was reached. Results show that the initial efficacy and safety of the tapering strategy were maintained up to three years. No relevant difference in the number of major flares was found between the tapering and usual care group. Disease activity, functioning and quality of life were also similar between groups and no significant difference in radiographic progression was found after three years. However, no other benefits (i.e. less adverse events) were observed.

In **chapter 2.2** a cost-effectiveness analysis performed on data of the DRESS long-term extension study shows that non-protocolised tapering (usual care group in the extension phase) is associated with higher cost and higher quality adjusted life year (QALY) loss,

compared to protocolised tapering (tapering group in the intervention phase), but that it still is cost saving compared to no tapering at all (usual care group in the intervention phase). Furthermore, in the tapering group, costs were slightly higher in the extension phase with QALY being roughly equal.

In the DRESS intervention phase, it was observed that minimal radiographic progression occurred more frequently in the tapering group. **Chapter 3** explores possible causes, including short-lived and major flares, disease activity and TNFi exposition. Findings demonstrate that radiographic progression is associated with disease activity, especially with swollen joint count, but only in the tapering group. This means that when the necessary causes (higher disease activity and tapering) are both present, a higher chance to develop radiographic progression occurs. Thus the need for tight control – already essential in the treatment of RA patients in general – is even more important when a tapering attempt is undertaken. Furthermore, radiographic progression should be monitored in patients tapering. With this finding, however, further progression is not to be expected in the future, since higher disease activity is a temporary side effect of the trial-and-error type of tapering strategy that was used in the DRESS study.

Although tapering of TNFi has been investigated extensively, data on tapering of other bDMARDs are scarce. Furthermore, most studies on tapering are clinical trials, leaving uncertainty on the effects of tapering in a daily clinical practice setting. **Chapter 4** researches whether tapering of abatacept and tocilizumab in a daily clinical practice setting is feasible and safe in a retrospective, explorative, controlled cohort study. The research compares patients with stable low disease activity in whom a tapering attempt was undertaken with patients with similarly stable low disease activity in whom no tapering attempt was undertaken. Tapering was attempted in 46% of abatacept patients and 70% of tocilizumab patients. After 12 months, in the abatacept group, 27% and 9% were successfully tapered and discontinued, respectively. In the tocilizumab group, 42% and 10% were successfully tapered and discontinued respectively. Tapering was maintained up to 72 months in one patient. DAS28 was significantly higher in the tocilizumab tapering group compared to the usual care group at six months but this difference disappeared at 12 months. For abatacept, disease activity was similar in the tapering group and usual care group during follow-up. All in all, it is shown that dose tapering of abatacept and tocilizumab in a daily clinical practice setting is feasible and seems clinically non-inferior to full dose continuation. However, numbers of patients in whom a tapering attempt was undertaken were suboptimal.

In the trial-and-error type of tapering strategy that was used in the DRESS study, flares are inevitable. If we would be able to predict which patient could successfully taper or discontinue and which patient could not, flares that are related to tapering could be prevented. Thus far, no clear predictors for successful tapering or discontinuation have been identified yet.[8] In **chapter 5**, two candidate predictors for successful tapering or discontinuation in the DRESS study are considered. The predictive value of the multi-biomarker disease activity (MBDA) score (**chapter 5.1**), measured at baseline (before tapering), for successful dose tapering or discontinuation, flare and radiographic progression was investigated. Baseline MBDA score was not predictive of successful tapering or discontinuation, occurrence of short-lived or major flare or radiographic progression. A borderline positive predictive value of baseline MBDA score for major flare was found in the usual care group, but this might well be a false positive finding due to multiple testing.

Baseline serum adalimumab or etanercept drug level or anti-drug antibodies (**chapter 5.2**) were also tested for their predictive value in the DRESS study. No clear predictive value for successful dose tapering or discontinuation was found, although subanalyses showed that adalimumab trough level was predictive of successful tapering. However, an inverse association was found between intermediate timed etanercept levels and successful tapering. These results again may reflect false positive findings, since the associations have opposite directions and the inverse association found for etanercept is incongruent with previous hypotheses.

Reflection

Knowledge on dose optimisation of bDMARDs in RA is expanding, but a few key points of discussion remain: 1) What is the best dose optimisation strategy in RA patients? 2) Can successful tapering or discontinuation of bDMARDS be predicted? 3) Which outcome measures should be used in dose optimisation studies? 4) How to improve implementation of bDMARD optimisation in daily clinical practice? 5) How do future developments affect the relevance of tapering in RA?

1. Dose optimisation strategies

Based on available evidence, the international guidelines on the management of rheumatoid arthritis have included a recommendation on tapering of bDMARDs, stating that tapering of bDMARDs may be considered when persistent remission is reached after glucocorticoids have been tapered.6 Tapering can especially be considered in patients using a concomitant csDMARD. In the light of this thesis, some remarks can be made on this recommendation.

1.1 Tapering versus discontinuation

The guideline starts with the recommendation to taper bDMARDs, which implies tapering instead of immediate discontinuation. Indeed, previous studies have shown that discontinuation without prior tapering is inferior to full dose continuation with regard to disease activity, functioning and radiographic progression, but that tapering is non-inferior to full dose continuation.[4] In the DRESS study a gradual tapering strategy was opted for with stepwise tapering until discontinuation or until a flare occurred. This strategy can be used to both identify patients who are able to discontinue their TNFi as well as patients who are able to taper, with the additional advantage of identifying different dosages in different patients. The disadvantage of this gradual tapering strategy is that in patients who are actually able to discontinue their TNFi, a tapering phase is still required prior to discontinuation. This is costly in both time and drug exposition. However, this can be counterbalanced by the fact that several studies, including the DRESS and DRESS long-term extension study, show that, on a whole, patients who are able to taper are more prevalent than patients who can discontinue their drug completely. Thus, savings of cost and medication in patients who are able to taper (but not discontinue) will be substantial as well.[7,9,10] It is not clear however, what tapering steps are the most optimal (gradual tapering in multiple steps or dose halving) and if and how they would differ for each bDMARD separately. In my opinion, a gradual disease activity guided tapering strategy in multiple steps is the most feasible, safe and cost-effective approach.

6

1.2 Remission versus low disease activity

The EULAR recommendations also state that patients should have reached persistent remission before tapering. However, clear consensus on which definition for remission to use is lacking. In previous studies with remission as inclusion criterion, several different definitions were used.[5] Nevertheless, I think that this statement can be disputed for several reasons. First, there is no clear evidence that tapering in patients considered to be in remission is superior to tapering in patients with low disease activity with regard to flaring. In fact, in this thesis, we have shown that tapering in patients with low disease activity is feasible and safe, with the exception of minimal radiographic progression in the tapering group. Second, when using persistent remission, implementation of tapering will be limited, without good reason, because persistent remission is only reached in a subset of patients (20-60% depending on the definition used).[11,12] Third, rheumatologists' adherence to a disease activity guided treatment protocol may be less when the target is remission instead of low disease activity.[13] Similarly, low disease activity is often considered an acceptable level by both patient and rheumatologist; at least it is the level at which a patient is considered well enough to continue the bDMARD without treatment alterations because of inefficacy. Lastly, in the DRESS study, disease activity at start of tapering was not a predictor for successful tapering or discontinuation.[7]

On the other hand, findings show a small but significantly higher radiographic progression score in patients who had tapered compared to patients who had not tapered in a low disease activity state and it could be hypothesized that this may not have occurred when patients in remission were included. However, other studies on TNFi tapering or discontinuation in patients with low disease activity did not find any difference in radiographic progression between groups.[14,15] Furthermore, the DRESS study identifies an association between mean time-weighted DAS28-CRP and mean radiographic progression. Baseline DAS28-CRP is not a confounder in this association. Thus, I conclude that low disease activity instead of remission as a prerequisite for tapering seems a safe and more clinically applicable approach.

1.3 Biologic versus conventional synthetic DMARD tapering or glucocorticoid tapering

Another point of debate is the order of tapering the different classes of drugs used in RA treatment. No studies have compared the safety and efficacy of tapering of steroids, csDMARDs and bDMARDs. Since glucocorticoids are associated with an increased risk of infections, osteoporosis and cardiovascular incidents, and are mostly used as escape drugs, it seems reasonable to taper them first.[16, 17]

With regard to csDMARDs and bDMARDs, there are several reasons why bDMARDs should be tapered first. An important argument is that bDMARDs are much more expensive than csDMARDs (400 to 1,500 versus 14,000 euro per patient per year in the Netherlands) and tapering of a bDMARD will thus lead to much bigger cost savings.[2] Also, bDMARDs therapy is associated with more severe infection compared to csDMARD therapy[1] and it requires injections or infusions, usually leading to more patient burden than oral administration as tablets. On the other hand, csDMARDs may be less well tolerated compared to bDMARDs and tapering of the csDMARD may therefore be attractive.18 Furthermore, bDMARD therapy is started when the csDMARD as monotherapy does not lead to sufficient disease control. Thus, the bDMARD may be the more effective drug and it might seem reasonable not to taper it, but to taper the csDMARD instead. Unfortunately, data on csDMARD tapering is limited with studies describing mostly mixed tapering of bDMARDs and csDMARDs and it is unclear whether csDMARDs can be tapered safely as well.[19-24] Since bDMARD tapering is much more extensively investigating and considering the high cost-savings, reduction of injections/infusions, and infections, it seems a rational choice to taper the bDMARD first.

The EULAR recommendation further states that tapering of a bDMARD should especially be considered in RA patients that use a concomitant DMARD. In my opinion, this is not a valid recommendation. Firstly, for some bDMARDs monotherapy is just as effective as combination treatment.[25-27] This is also true in other diseases than RA, for instance in psoriatic arthritis and spondyloarthritis. Furthermore, in previous studies, concomitant csDMARD use was not a predictor for successful tapering or discontinuation.[8]

All in all, bDMARD tapering prior to csDMARD tapering seems reasonable, especially with regard to cost-savings, but further studies are needed to investigate whether csDMARD tapering may be safe as well. In fact, one study is currently being executed, comparing tapering of a bDMARD or methotrexate in patients on combination therapy.[28] Furthermore, future studies should focus on whether it is indeed equally safe and effective to taper a bDMARD in patients that do or do not use a concomitant csDMARD.

1.4 Failed tapering attempts

What is not mentioned in the EULAR recommendations is what to do when a tapering attempt has failed. One should bear in mind that dose optimisation does not solely mean tapering or discontinuation but also reinstallment or re-escalation of the drug when a patient is not doing well. Although this has not been investigated separately, stepwise backward re-escalation until the lowest effective level seems a face valid, effective and safe method and would have more advantages than directly restarting the bDMARD at the registered dose and then tapering again in an attempt to find the lowest dose, because the latter will require more medication. On the other hand, the stepwise backward re-installment could lead to longer flaring. However, the results of the DRESS study (non-inferiority of prolonged flaring in the tapering group compared to patients not tapering) have shown that this is not the case.

It is also unclear whether multiple tapering attempts should be undertaken. Undertaking a second tapering attempt after a first tapering attempt has proven unsuccessful would only be useful when the dose-response curve within a patient changes over time. Since a small proportion of patients develop secondary inefficacy and flare after long-term use of a bDMARD, this obviously occurs in some patients. In the DRESS study, multiple tapering attempts were not advised. The study shows that in patients attempting to taper, a temporary rise in disease activity caused by the tapering attempt is associated with radiographic progression. Since multiple unsuccessful tapering attempts could lead to more frequent rises in disease activity, one could hypothesize that this would lead to more radiographic progression, but no data is available yet. In the STRASS trial, patients were allowed to attempt to taper more than once with no differences between the tapering and full dose continuation groups with regard to disease activity and radiographic progression.[29] However, in only thirteen percent of patients randomised to taper a second tapering attempt was undertaken.

I therefore conclude that as of yet insufficient data is available on the effects of multiple tapering attempts and further research addressing this topic is warranted.

2. Prediction

The prediction of successful tapering or discontinuation has at least two conceptual advantages above treat-to-target tapering: 1) In patients predicted not to be able to taper, no tapering attempt will be undertaken at all, thus preventing flare, and 2) In patients predicted to be able to successfully discontinue their bDMARD, direct discontinuation is possible without having

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to taper first, thus saving time and medication. Identification of patients in whom tapering or discontinuation will be successful may also optimize implementation of tapering since both patients and physicians will be more eager to initiate tapering. In previous studies, clinical parameters and other biomarkers have not shown to be predictive for successful tapering or discontinuation with the exception of shorter symptom duration at the start of the bDMARD, which was associated with successful discontinuation.[8] Furthermore, lower baseline Sharp-van der Heijde erosion score and higher adalimumab trough level (the latter was described in this thesis) were associated with successful tapering.[8] Although interesting, these were mostly weak associations found in low quality studies. Furthermore, many studies on possible predictors did not follow the appropriate guidelines (for instance the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guideline) for reporting of prediction research.[30] Also, as mentioned previously, these studies showed heterogeneity in both design and outcome measures. Lastly, underreporting of negative results may be a problem and this may lead to overestimation of the found associations. Thus, no clear predictors for successful tapering or discontinuation are known yet.

2.1 Multi-biomarker disease activity score

In this thesis two types of serum biomarkers that could be interesting to predict successful tapering or discontinuation were tested. First, we investigated the predictive value of the MBDA score for successful tapering or discontinuation in the DRESS study. Biomarkers have been suggested to have a smaller measurement error than DAS28 and to be more feasible and less costly. However, measurement error of most biomarkers has shown to be comparable to the measurement error of the DAS28 (around twenty percent)[31] and most biomarkers have to be measured in specialized laboratories. This takes time and is expensive. Another important disadvantage of biomarkers is that they only measure inflammation without taking the patient perspective into account.

The MBDA score was previously tested as being predictive for radiographic progression in early RA patients.[32] Furthermore, one study showed that the MBDA score was predictive for relapse after tapering of bDMARDs, csDMARDs and steroids in RA patients in sustained remission.[33] The predictive value improved when the MBDA score was combined with ACPA (anti citrullinated peptide antibody) status. Another study showed that the MBDA score was a modest predictor for flare after TNFi discontinuation.[34] The DRESS study could not demonstrate any predictive value of baseline MBDA score for successful tapering or discontinuation. Although direct comparison of results is difficult due to the different tapering strategies and different definitions for flare, a usable predictor should work in all relevant contexts; just like ACPA testing is associated with more severe RA outcomes in all cohorts around the world. Furthermore, although the measurement error of the MBDA score has shown to be somewhat lower as compared to DAS28 (10 percent versus twenty percent)[31,35], other potential benefits like cost- and time-savings are not present for the MBDA score since a single MBDA measurement costs around €600 and takes two weeks, whereas a full 28-joint count can be estimated to cost around €20 (time and personnel required to measure joints and CRP) and takes only 90 seconds.36 Based on the results in this thesis and the above-mentioned arguments, I can conclude that the MBDA score is not useful as a predictor for successful tapering of TNFi in rheumatoid arthritis patients.

2.2 Serum TNFi drug level and antibodies

Other serum biomarkers that were tested in this thesis as possible predictors of successful tapering or discontinuation were TNFi drug levels and anti TNFi antibodies. In previous studies, TNFi drug levels have been shown to be cross-sectionally associated with response. However, a clear predictive value has not been demonstrated yet. In this thesis, we did not find a clear association between drug level and successful tapering. This could be explained by the fact that although an association between drug level and disease activity may be present, dose-response curves vary too much on an individual level.[37] This means that the same drug level can be supratherapeutical for one patient but subtherapeutical for others. It has also been suggested that the inflammation process itself as well as some co-medications may influence pharmacokinetics of TNFi, meaning that other drug levels are required for different disease activity levels and different co-medications.[38] Furthermore, in the DRESS study, patients who were able to discontinue their drug were also included. In these patients, no association between baseline drug level and disease activity may be present at all, since these patients would do well without the drug.

However, an association between successful tapering and adalimumab trough level was found. Although this association might reflect reality, it could also be a false positive finding caused by multiple testing, especially since we found an inverse association for (intermediate timed) etanercept level and successful tapering (lower intermediate timed etanercept level was predictive of successful tapering). Other studies are needed to replicate these results, since there is lack of other data on this subject.[39] This should include a trial that examines disease activity guided tapering compared to disease activity guided tapering combined with drug level and/or anti-drug antibodies guided tapering.

With regard to anti-drug antibodies, no association between the presence of antibodies at baseline and successful tapering is found in the DRESS study, but prevalence of antidrug antibodies was low. Previously, claims have been made on the development of antibodies after tapering, although no studies have found this association yet. DRESS only measured the presence of anti-drug antibodies before tapering. Other studies should investigate whether antibodies actually increase after tapering. It still remains the question, however, what the clinical utility of the detection of anti-drug antibodies would be, since there is no treatment for anti-drug antibodies and the only option when detecting antibodies is to switch to another bDMARD. Furthermore, if clinically relevant development of antibodies after tapering does occur, one might expect that it would be more difficult to regain low disease activity after re-installment or re-escalation of the bDMARD. However, in the DRESS and DRESS long-term extension study, disease activity remained low during study course and in patients that had experienced a flare, low disease activity was regained after re-installment or re-escalation of the bDMARD.

2.3 Imaging

Besides serum biomarkers, imaging techniques could also be interesting candidate predictors as it can be hypothesized that they can detect subclinical inflammation. In RA patients that were classified as being in clinical remission, previous studies found that the presence of persistent subclinical synovitis, detected by ultrasound (doppler) or MRI (bone marrow edema), is associated with an increased risk of relapse and radiographic progression, respectively.[40-44] Recent studies have also shown some potential for ultrasound to predict which patients are able to taper.[45-47] Furthermore, previously, PET-CT scanning has shown to be able to detect subclinical synovitis in RA patients in clinical remission.[48] Currently, a sub study of the DRESS study is being performed, investigating the value of 18F-FDG PET-CT scanning as possible predictor for successful tapering or discontinuation.

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In conclusion, at this moment, no clear predictors of successful tapering are known yet. Until predictors are identified, tight control remains of the utmost importance. Nevertheless, the disease activity guided trial-and-error type of dose optimisation used in this thesis already seems a very safe and cost-effective approach. Furthermore, since a previous study has shown that for a predictor of successful tapering to be cost-effective, it needs to have a very high sensitivity and specificity (96% or higher), it may be impossible to find at all.[49]

3. Outcome measures

Previous studies on dose optimisation show great heterogeneity in outcome measures and it can be debated what the most optimal outcome measures are.

3.1 Flare criteria

There is little consensus in dose optimisation studies on which definition of flare to use, which is reflected in the different definitions mentioned in these studies, including loss of response, loss of (deep) remission or low disease activity.50 In the DRESS study the use of an OMERACT (Outcome Measures in Rheumatology Clinical Trials) validated DAS28 based flare criterion was chosen.[51] Although this criterion has shown to have the best construct and criterion validity and it is easy to use, it is solely based on DAS28 worsening. The last few years, a new and broader flare criterion is being developed by the OMERACT flare group that also includes patients' and rheumatologists' perspectives and currently, DRESS data is being used to validate this flare criterion.[52, 53] When validation of this flare criterion is completed, it will hopefully lead to uniformity in outcome measures, which is of the utmost importance to be able to compare results between studies on dose optimisation of bDMARDs in RA.

The flare criterion that was used in this thesis was originally validated using erythrocyte sedimentation rate (ESR). However, in this thesis, both DAS28 based on ESR and C reactive protein (CRP) has been used. This was caused by the fact that a more rapid measurement of CRP became available, making it more convenient to measure DAS28-CRP than -ESR at our outpatient clinic. More importantly, CRP has shown to be more sensitive to change and is less affected by other confounding factors.[54] However, DAS28-CRP and –ESR are not completely interchangeable since DAS28-CRP values are proven to be lower compared to DAS28-ESR when measuring disease activity and DAS28-CRP will show more improvement when measuring change in disease activity compared to DAS28-ESR.[55-58] Therefore, a recently published study suggested more stringent cut-off values for low disease activity when using DAS28-CRP.[59] Based on these cut-off values, the flare criterion in the long-term extension study was altered accordingly. It could be hypothesized that this influences outcomes in the DRESS long-term extension. However, it is unclear how this would have affected outcomes, since tight control would have become even tighter, and this would have occurred in both the usual care and tapering group.

3.2 Persistence of successful tapering or discontinuation

Data on long-term effects after tapering, as well as data on persistence of successful tapering or discontinuation, are scarce. In the long-term extension study of the DRESS study, 29% of patients in the tapering group persisted being successfully tapered and 17% of patients in the tapering group persisted being bDMARD free with maintenance of low disease activity during the extension phase. These numbers are very comparable to the outcomes of the STRASS extension study: successful tapering that persisted up to three years after the original trial was possible in 30% and successful discontinuation was possible in 12% of patients. In the

SONATA study, we found that successful tapering of abatacept and tocilizumab was persistent, even up to six years in one patient. This suggests that in a subset of patients, bDMARDS can be continued on a lower dose or longer interval for a significant period of time, consequently leading to a longer reduction in patient burden as well as costs. However, whether mean disease activity over time remains low and subsequently no increase in radiographic progression occurs should be investigated, both for abatacept and tocilizumab as well as for all other bDMARDs.

3.3 Radiographic progression

Another important outcome measure in this thesis was radiographic progression. We found that the difference in mean radiographic progression between the tapering and usual care group over eightteen months was 0.6 Sharp-van der Heijde points. This is well below the previously suggested cut-off level of what is minimally clinically important (minimal clinical important change, MCIC: five points per year).[60, 61] Nevertheless, even minimal radiographic progression may become clinically relevant if progression lingers on in subsequent years. We found that the additional progression in DRESS was caused by a higher disease activity in patients that had attempted to taper and hypothesized that this could be caused by the disappearance ('disconnect') of the inhibitory effect of TNFi on radiographic progression, so that when TNFi is tapered, disease activity resumes to drive the development of radiographic progression. Although we investigated radiographic progression in the DRESS long-term extension study, no direct comparison of the tapering group and usual care group was possible over three years, since tapering was also allowed in the usual care group after the first eightteen months. Nevertheless, in the extension phase, radiographic progression was not significantly different between groups and tapering outside of a controlled trial setting seems safe with regard to radiographic progression. In my opinion, and based on the studies included in this thesis, tapering will probably not induce clinically significant radiographic progression. Other studies are required to investigate whether radiographic progression will stabilize or will progress further in the long term.

3.4 Adverse events

Important outcomes when tapering also include adverse events. We hypothesized that tapering of a bDMARD will lead to less adverse events, like infection or skin malignancy. For serious infections, full dose bDMARD use is associated with an increase of 0.6% per patient per year and this risk may be lowered when the bDMARD is tapered. On the other hand, TNFi use has shown to have a protective effect on the development of cardiovascular disease and osteoporosis (probably by inhibiting the systemic inflammatory process)[62-65] and inversely, a raised CRP in patients with polyarthritis is associated with cardiovascular death.[66] Thus one can also hypothesize that cardiovascular incidents and osteoporosis might increase in patients tapering their TNFi. However, when combining the potential risks and benefits of TNFi use, the risk reduction of cardiovascular disease and osteoporosis is probably (at best) equal to the risk increase on serious infections.[1, 65, 67] Furthermore, a previous study showed that when patients are kept at low disease activity, the risk of cardiovascular events remains reduced.[68] In the DRESS study, this prerequisite was met, since patients were closely monitored to maintain a state of low disease activity during tapering. Therefore, the numbers needed to harm for cardiovascular incidents and osteoporosis after tapering bDMARDs are probably higher than the number needed to treat to lower the risk of infection by bDMARD tapering.

In this thesis we could not confirm any differences in adverse events between patients

6

tapering and not tapering, both in the DRESS long-term extension study, as well as the SONATA study. This could be explained by underreporting of adverse events, and by the low incidence of important adverse events. Furthermore, in both the DRESS LTE and SONATA study, an inclusion criterion was that patients should have used their bDMARD for more than six months at baseline. This could have caused a phenomenon called 'healthy survivor bias': patients that experience adverse events on a particular bDMARD are more likely to have been switched to another bDMARD quickly. Thus these patients would not have been included in our studies. Nevertheless, data on adverse events in patients tapering their bDMARD are scarce, although one study on tapering of etanercept found a significantly lower number of infections in patients that had tapered.[69] On the other hand, another study comparing disease activity guided optimisation of TNFi with full dose continuation did not find a difference in adverse events between groups. Future studies should pay attention to adverse events in patients tapering their bDMARD, especially focusing on infections, malignancy and cardiovascular incidents.

3.5 Cost effectiveness

It seems logical that medication reduction will lead to cost reduction, but disease activity guided dose optimisation requires frequent monitoring and causes an increase in short-lived flares. This may lead to a lower quality of life and higher cost due to work absenteeism and more outpatient visits. However, cost-effectiveness analyses of the original DRESS study showed that the majority of costs were driven by medication cost and not so much by extra outpatient clinic visits or RA-related absence from work. There was a small QALY loss in the tapering group. However, even after adjustment to account for the upper limit of what society (in the Netherlands) is willing to pay or accept as costs per QALY, net savings were still high. Cost-effectiveness analyses during the extension phase showed that cost effectiveness is maintained over three years, although medication cost rose slightly during the extension phase, which is explained by a slightly higher use of TNFi during the extension phase. This may be a reflection of the fact that in the induction phase, tapering was attempted in all patients randomised for tapering and not only successful, but also failed tapering attempts will account for less medication use.

At the moment, prices of several bDMARDs as well as bsDMARDs have decreased, but sensitivity analyses showed that cost effectiveness is maintained even with significant price reductions.[2] All in all, I expect that disease activity guided bDMARD tapering will remain very cost-effective in the future with protocolised tapering being slightly more cost-effective than non-protocolised tapering. Although these cost savings will not directly benefit RA patients, they will benefit the health care system and society in general.

4. Implementation

To be able to successfully implement dose optimisation into a daily clinical practice setting, certain conditions should be met first, including: 1) General terms and conditions, 2) Patient associated barriers and facilitators and 3) Rheumatologist associated barriers and facilitators.

4.1 General terms and conditions

An important prerequisite for RA care is the ability to regularly monitor patients to keep disease activity as low as possible and make treatment alterations when necessary (the previously mentioned 'tight control' and ' treat-to-target'). Although tight control is clearly superior over regular follow-up[70], studies have also shown that implementation of tight

control sometimes is suboptimal. Several reasons have been mentioned, including time-consuming measurements (although, as mentioned previously, measurement of DAS28 actually only takes 90 seconds)[36], long distance of a patient to the hospital and hesitance of rheumatologists to use composite scores to measure RA disease activity.[71-73] Although some of these circumstances may be difficult to alter, it is important to recognize them and investigate what can be improved.

4.2 Patient associated barriers and facilitators

To successfully implement dose tapering, it is important to investigate patients' preferences, especially since patients' preferences regarding treatment options often differ from those of physicians.[74] In the SONATA study, implementation of tapering was clearly suboptimal since all patients included were considered eligible to taper, but in 35% of these patients no tapering was initiated. It was not possible to investigate whether this was caused by patient- or rheumatologist associated barriers or facilitators. This is in line with another study on tapering where the authors observed that up to 40% of patients refused to participate.[75] It was speculated that this was related to fear of losing remission state and the impact this would have on work participation and quality of life. However, Verhoef et al investigated that 75% of patients actually did have favourable views on tapering with the most important points being (amongst others): trusting their treating rheumatologist, fear of flaring and the possibility to restart the tapered drug.[76]

Other important phenomena to consider in tapering are the 'nocebo effect' and 'incorrect causal attribution', causing patients to think that 1) tapering is inferior to full dose continuation and therefore disease deterioration may be perceived more often or earlier and 2) in case of flare symptoms they will attribute these symptoms to the tapering attempt, although flares naturally also occur every once in a while in the disease course, unrelated to treatment alterations.[77] This is similar to effects seen after transitioning from an originator bDMARD to a biosimilar DMARD (bsDMARD).[78,79]

Possible facilitators can be found in investigating what makes tapering appealing to a patient. We hypothesized that tapering of subcutaneous abatacept or tocilizumab may be more successful than tapering of intravenous abatacept or tocilizumab, since less frequent self-injection is a more directly noticable advantage compared to lowering the dose. This has been underlined by a recent study showing that tapering of subcutaneous tocilizumab by injection spacing was more successful than lowering the dose of intravenous tocilizumab.[80] However, tapering of subcutaneous TNFi could also be more successful because overall the subcutaneous formulation contains eight percent more drug than the intravenous formulation. It would be interesting whether protocol adherence nowadays is higher in patients using subcutaneous abatacept or tocilizumab compared to patients using intravenous abatacept or tocilizumab.

It is known that physicians often underestimate patients' desire for information[74] and informing patients has shown to be a very effective intervention in a different patient population in whom physicians want to taper drugs as well: in a study on patients using benzodiazepines, a single intervention by either an information letter or a GP consultation decreased benzodiazepine use.[81] Thus, paying extra attention on adequately informing a patient can be very effective. To develop confidence in tapering, it may be a good strategy to inform patients already at the start of their first bDMARD that tapering may be considered at some point in the future.

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4.3 Rheumatologist associated barriers and facilitators

For a large proportion, the same barriers and facilitators for patients are present in rheumatologists. They should be convinced that dose optimisation is non-inferior to full dose continuation and training may help in this process, since training of rheumatologists has shown to improve protocol adherence to treat-to- target as well as dose optimisation.[82-84] In the SONATA study, the suboptimal number of patients in whom a tapering attempt was undertaken, may be a matter of timing, since during the last few years, several interventions took place to train rheumatologists in disease activity guided tapering and the increasing experience will improve protocol adherence. This is underlined by the fact that in the DRESS long-term extension study in the former usual care group, in the majority of patients a tapering attempt was undertaken, although during the extension phase no specific tapering advice was given, with results on efficacy and safety being comparable to results of the original tapering group during intervention phase. Thus, experience with a stringent tapering advice may increase protocol adherence.

In a previous study on tapering in a daily clinical practice setting, evident differences between rheumatologists were identified on whether, when and in whom tapering should be attempted and several different patient characteristics are being weighted in this consideration.85 In general, despite treatment guidelines and protocols, it seems that opinions on which patient to taper vary widely. Future studies should investigate these different rheumatologist associated characteristics and this may be helpful in refining treatment guidelines and optimising protocol adherence.

5. Future developments

An important development is the introduction of the bsDMARDs. These drugs are highly similar to the original bDMARDs. Studies with etanercept, infliximab and rituximab bsDMARDs have shown that these drugs are equivalent to their original counterpart, also with regard to efficacy and safety.[86-88] Although treatment with bDMARDs will become less expensive, it is to be expected that even with a significant cost reduction, dose tapering will still be cost-effective, and tapering will remain a relevant treatment strategy.

It seems logical that in general, tapering of chronically used drugs is also relevant outside of RA and other rheumatic inflammatory diseases. For instance, in inflammatory bowel diseases, dose optimisation of bDMARDs and csDMARDs is a topic of interest, although it is not specifically covered in international guidelines yet and published data on dose optimisation mostly consists of retrospective cohort studies.[89] Thus, randomised clinical trials are needed to investigate efficacy and safety of tapering of bDMARDs In other inflammatory diseases and in fact at the moment three trials are being executed on tapering of TNFi in Crohn's disease and psoriasis.[90-92] However, many chronic diseases share similarities with inflammatory diseases with regard to chronic medication use and associated costs, adverse events and patient burden. Therefore, the knowledge that is gained in this thesis on RA may thus have a much wider scope.

Conclusions and implications

This thesis has a number of implications for the use of disease activity guided dose optimisation of bDMARDs in RA patients in daily clinical practice:

- Disease activity guided tapering and discontinuation of adalimumab, etanercept, abatacept and tocilizumab appears to be feasible and safe in RA patients.
- Tapering of TNFi in RA patients is highly cost-effective and remains cost-effective outside of a study protocol.
- Tapering of TNFi in RA patients requires tight control to keep disease activity as low as possible and to prevent radiographic progression.
- The MBDA score as well as serum TNFi levels and anti-TNFi antibodies are no useful predictors for successful tapering or discontinuation of TNFi in RA patients.
- Protocol adherence for tapering of bDMARDs in RA patients in daily clinical practice is suboptimal.

Research agenda

Although this thesis contributes to the existing body of knowledge on dose optimisation in RA patients, some questions remain unanswered. Future research should address the following topics:

- Identifying the most optimal dose optimisation strategy for each bDMARD
- Investigating whether bDMARDs or csDMARDs should be tapered first
- Further validating and reaching consensus on a flare criterion that can be widely used in dose optimisation studies
- Comparing disease activity guided dose optimisation with drug level and/or anti-drug antibody guided dose optimisation
- Investigating laboratory or imaging markers as possible predictors for successful dose optimisation
- Exploring facilitators and barriers of dose optimisation for both patients as well as rheumatologists
- Investigating efficacy, safety and cost-effectiveness of dose optimisation of drugs in other inflammatory (i.e. spondyloarthritis, psoriatic arthritis or inflammatory bowel diseases) or non-inflammatory chronic diseases

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6

Nederlandse samenvatting

Hoofdstuk 1: Algemene inleiding

Reumatoïde artritis (RA) is een chronische ontstekingsziekte van de gewrichten. De meeste patiënten met RA ontwikkelen een symmetrische gewrichtsontsteking, waarbij de kleine handgewrichtjes het vaakst zijn aangedaan. De ziekte komt meer voor bij vrouwen dan bij mannen. Gewrichtsontstekingen leiden tot verminderd functioneren, verlies van kwaliteit van leven en in een deel van de patiënten tot gewrichtsschade. Voor de behandeling van RA is een aantal soorten medicijnen beschikbaar. Een belangrijke soort van medicijnen zijn de zogenaamde biologische reumaremmers (biologic disease modifying anti-rheumatic drugs, bDMARDs). Deze medicijnen konden aan het eind van de vorige eeuw worden ontwikkeld door een beter inzicht in het onderliggend ontstekingsproces van RA. Binnen deze bDMARDs zijn tumor necrose factor blokkers (tumor necrosis factor inhibitors, TNFi) de meest gebruikte middelen. Deze middelen worden per infuus (intraveneus) of (meestal) door de patiënt zelf per onderhuidse (subcutane) injectie toegediend.

Hoewel bDMARDs effectief en veilig zijn, gaat het gebruik van deze middelen gepaard met een iets hogere kans op bijwerkingen, waaronder ernstige infecties en huidkanker. Daarnaast zijn bDMARDs veel duurder dan de vroegere reumaremmers (conventional synthetic disease modifying antirheumatic drugs, csDMARDs). Om bijwerkingen en kosten te verminderen, is de laatste jaren veel onderzoek gedaan naar het afbouwen van bDMARDs of zelfs stoppen ervan in RA patiënten bij wie de ziekte rustig is. Afbouwen kan op twee manieren, namelijk door de dosering van de bDMARD te verlagen of door de periodes tussen de toedieningen van de bDMARD te verlengen.

In dit proefschrift worden de korte en lange termijn effecten van het afbouwen van TNFi bestudeerd alsmede de haalbaarheid en veiligheid van het afbouwen van andere bDMARDs in de dagelijkse praktijk. Verder wordt onderzocht of van te voren voorspeld kan worden wie succesvol een bDMARD kan afbouwen of zelfs stoppen.

Hoofdstuk 2: Lange termijn effecten van afbouwen van TNF blokkers

In dit hoofdstuk wordt beschreven wat de lange termijn uitkomsten zijn van het afbouwen van TNFi. Hiervoor is gekeken naar de lange termijnuitkomsten van een eerder gepubliceerde studie: de DRESS (Dose REduction Strategies of Subcutaneous TNF inhibitors) studie. In deze studie, die tussen 2011 en 2014 plaatsvond, werden 180 patiënten met langdurig (tenminste 6 maanden) rustige RA geïncludeerd. In 120 patiënten werd op proef geprobeerd de TNFi af te bouwen door stapsgewijs de periode tussen de injecties langer te maken. Deze afbouwgroep werd vergeleken met 60 RA patiënten met rustige ziekte waarin de TNFi niet werd afgebouwd (standaardzorggroep). Het afbouwen gebeurde stapsgewijs door iedere 3 maanden het tijdsinterval tussen de injecties langer te maken. Deze stappen werden doorlopen tot een patiënt helemaal kon stoppen of totdat er een opvlamming van de reuma (flare) optrad. Bij een flare werd het tijdsinterval tussen de injecties weer verkort, of, indien de patiënt gestopt was, werd de TNFi hervat. Patiënten werden daarvoor gedurende 18 maanden tenminste driemaandelijks gecontroleerd waarbij de ziekteactiviteit werd vastgelegd middels de DAS28 (een samengestelde score bestaande uit het aantal pijnlijke en gezwollen gewrichten, de ontstekingswaarde in het bloed en een beoordeling van de patiënt van zijn algemene gezondheid).

Uit de DRESS studie is gebleken dat het afbouwen van TNFi in RA patiënten met rustige ziekte non inferieur is aan (of te wel niet slechter is dan) niet afbouwen. Wel kwamen kortdurende flares vaker voor in patiënten bij wie was afgebouwd vergeleken met patiënten waarbij niet was afgebouwd. Daarnaast was er in de afbouwgroep sprake van iets meer gewrichtsschade

zichtbaar op röntgenfoto's. Tot slot was afbouwen duidelijk kosteneffectief. Hoewel deze uitkomsten veelbelovend waren, is het de vraag of afbouwen van TNFi ook op de lange termijn veilig en effectief is.

Hoofdstuk 2.1

In dit hoofdstuk wordt onderzocht of de korte termijn resultaten van 18 maanden van de DRESS studie behouden blijven tot 36 maanden. Van belang daarbij is dat er in de DRESS studie alleen patiënten in de afbouwgroep hun TNFi mochten afbouwen. In deze lange termijn studie (extensiefase, van 18-36 maanden) mocht de reumatoloog in overleg met de patiënt in zowel de afbouwgroep als de standaard zorg groep zelf bepalen of een afbouwpoging ondernomen werd.
De belangrijkste uitkomstmaat was het optreden van een langdurige flare (gedefinieerd als een flare die meer dan 3 maanden duurde). In de extensiefase trad er in 10% van de patiënten in de afbouwgroep en in 12% van de patiënten in de standaardzorggroep een langdurige flare op. Dit is niet significant verschillend. Gedurende de gehele periode van 3 jaar trad er in 17% van de patiënten in de afbouwgroep een langdurige flare op en in 14% van de patiënten in de standaardzorggroep. Ook dit is niet significant verschillend. Ten aanzien van kortdurende flares, kwamen deze in de oorspronkelijke DRESS studie vaker voor in de afbouwgroep. In de extensiefase is er geen verschil in kortdurende flares tussen de afbouwgroep en de standaardzorggroep. Daarnaast is er in de extensiefase geen verschil in ziekteactiviteit, functioneren en kwaliteit van leven tussen de studiegroepen. Van tevoren was verondersteld dat er mogelijk minder bijwerkingen zouden optreden in de afbouwgroep. Dit wordt echter in dit onderzoek niet bevestigd. Wel kan uit dit onderzoek worden geconcludeerd dat afbouwen ook haalbaar en veilig is als er een afbouwpoging wordt ondernomen als dit door de behandelend reumatoloog in overleg met de patiënt zelf bepaald mag worden (dus zonder een leidend onderzoeksprotocol).

Hoofdstuk 2.2

Een van de belangrijkste redenen om bDMARDs af te bouwen, is omdat deze medicijnen duur zijn. In de DRESS studie was reeds onderzocht dat het afbouwen van TNFi kosteneffectief is. In hoofdstuk 2.2 wordt aangetoond dat afbouwen ook op de lange termijn kosteneffectief is, zonder duidelijk verschil in kwaliteit van leven ten opzichte van niet afbouwen. In de oorspronkelijke afbouwgroep blijft de kosteneffectiviteit behouden in de extensiefase. Wel stijgen de kosten in de oorspronkelijke afbouwgroep, waarschijnlijk omdat sommige patiënten uiteindelijk toch weer op een hogere dosering TNFi uitkomen, en omdat op proef afbouwen geld scheelt, ook als het niet succesvol blijkt. In de standaardzorggroep is de kwaliteit van leven tijdens de extensiefase wat slechter en zijn de kosten hoger (gemiddeld 4000 euro meer per patiënt per 18 maanden) dan in de afbouwgroep tijdens de interventiefase. Dit kan worden verklaard doordat er tijdens de interventiefase volgens een strikt onderzoeksprotocol werd afgebouwd. Als een reumatoloog zelf mag bepalen om af te bouwen, dan is dit dus minder kosteneffectief dan wanneer er wordt afgebouwd volgens een strikt onderzoeksprotocol. Als er door de reumatoloog zelf bepaald mag worden of er wordt afgebouwd, dan is dit echter nog steeds beduidend meer kosteneffectief dan helemaal niet afbouwen (gemiddeld bijna 6000 euro kostenbesparing per patiënt per 18 maanden).

Hoofdstuk 3: Röntgenschade na afbouwen van TNF blokkers

In de DRESS studie was geconstateerd dat radiologische gewrichtsschade (gewrichtsschade zichtbaar op röntgenfoto's), wat meer voorkwam in patiënten bij wie de TNFi was afgebouwd. Hoewel het ging om minimale gewrichtsschade over een periode van 18 maanden, zou deze schade wel relevant kunnen worden in de toekomst als het zich voortzet. In hoofdstuk 3 worden drie potentiële oorzaken voor het ontwikkelen van radiologische gewrichtsschade in de DRESS studie onderzocht. Er zou meer gewrichtsschade kunnen zijn ontstaan omdat 1) er vaker flares voorkwamen in de afbouwgroep, 2) de ziekteactiviteit gemiddeld genomen hoger was in de afbouwgroep of 3) er minder blootstelling was aan het medicijn in de afbouwgroep, terwijl we weten dat het medicijn juist beschermt tegen ontstaan van schade.
Uiteindelijk blijkt alleen de gemiddelde ziekteactiviteit in de afbouwgroep geassocieerd te zijn met radiologische gewrichtsschade. Hiervan is met name het aantal gezwollen gewrichten geassocieerd met radiologische gewrichtsschade in patiënten bij wie de TNFi is afgebouwd. Dit betekent dat deze patiënten nauwgezet gecontroleerd moeten worden om de ziekteactiviteit zo laag mogelijk te houden.

Hoofdstuk 4: Afbouwen van abatacept en tocilizumab

Hoewel er veel onderzoek is gedaan naar het afbouwen van TNFi, is het afbouwen van andere bDMARDs zoals abatacept en tocilizumab minder bestudeerd. Daarnaast is er vooral veel bekend over het afbouwen van bDMARDs in onderzoeksverband. In hoofdstuk 4 wordt gekeken naar het afbouwen van abatacept en tocilizumab in de dagelijkse praktijk. Uit dit onderzoek blijkt dat er maar in 46-70% van de patiënten met rustige ziekteactiviteit (die voldoen aan de voorwaarden voor veilig afbouwen) daadwerkelijk een afbouwpoging wordt gedaan. Van de patiënten bij wie een afbouwpoging wordt ondernomen, is na een jaar 27-42% succesvol afgebouwd en ongeveer 10% succesvol gestopt. Sommige patiënten kunnen langdurig afgebouwd blijven, waarbij één patiënt zelfs zes jaar afgebouwd kan blijven. Ziekteactiviteit en functioneren zijn vergelijkbaar tussen patiënten die hebben afgebouwd en patiënten die niet hebben afgebouwd. Ook in dit onderzoek kan niet worden geconcludeerd dat afbouwen leidt tot minder bijwerkingen.

Hoofdstuk 5: Voorspellers van succesvol afbouwen of stoppen

Tot nu toe werd in RA patiënten met rustige ziekte op proef geprobeerd om af te bouwen. Als echter van te voren voorspeld kan worden wie succesvol kan afbouwen of stoppen, heeft dit twee belangrijke voordelen:
1. In patiënten met een hoge kans op succesvol kunnen stoppen, hoeven niet eerst alle afbouwstappen doorlopen te worden, maar kan direct gestopt worden. Dit scheelt tijd en medicatie.
2. In patiënten met een hoge kans dat ze niet succesvol kunnen afbouwen of stoppen, kan beter geen afbouwpoging ondernomen te worden. Dit scheelt flares. In hoofdstuk 5 worden 2 kandidaat voorspellers getest.

Hoofdstuk 5.1

De multi-biomarker (multibiomarker disease activity, MBDA) score is een bloedtest die is ontwikkeld om de ziekteactiviteit van RA te meten. Deze MBDA score zou toegevoegde waarde kunnen hebben ten opzichte van de reguliere manier van het meten van ziekteactiviteit in RA middels de DAS28. Verondersteld wordt dat de MBDA score ziekteactiviteit zou kunnen opsporen die met de DAS28 gemist wordt. Daarnaast zou het meten van de MBDA score

simpeler zijn dan het meten van een volledige gewrichtsscore, omdat er geen poliklinisch contact met een reumatoloog nodig is. Voorts is de MBDA score in andere onderzoeken beschreven als mogelijke voorspeller van radiologische gewrichtsschade in patiënten die recent gediagnosticeerd zijn met RA. In dit hoofdstuk wordt gekeken of de MBDA score in de DRESS studie voor start van afbouwen zou kunnen voorspellen bij welke patiënten de dosering succesvol afgebouwd of gestopt kan worden. Dit kan echter niet worden aangetoond. Daarnaast is er ook geen voorspellende waarde van baseline MBDA score voor het ontwikkelen van radiologische gewrichtsschade of flares in patiënten die hun TNFi hebben afgebouwd, met uitzondering van flares in de standaardzorggroep. Deze laatste bevinding is mogelijk een fout positieve bevinding, doordat meerdere hypothesen worden getest. De kans is dan groter dat er bij toeval een positieve bevinding wordt gedaan. Wij concluderen hieruit dat het meten van de MBDA score voor de start van afbouwen niet zinvol is om te voorspellen welke RA patiënten hun TNFi succesvol kunnen afbouwen of stoppen.

Hoofdstuk 5.2

Uit eerder onderzoek is gebleken dat de hoogte van medicatiespiegels van TNFi en antistoffen gericht tegen TNFi in het bloed van RA patiënten is geassocieerd met het wel of niet reageren op TNFi. Daarop is verondersteld dat medicatiespiegels en antistoffen voorspellend zouden kunnen zijn voor succesvol afbouwen of stoppen. De achterliggende gedachte hierbij is dat patiënten met een hoge medicatiespiegel wellicht ook met een lagere spiegel (dus minder medicijn nodig) hetzelfde effect behouden (en dus zouden kunnen afbouwen). Daarnaast zou in patiënten bij wie helemaal geen medicatiespiegel wordt gedetecteerd (onder andere bijvoorbeeld doordat het medicijn wordt weggevangen door antistoffen) terwijl ze wel lage ziekteactiviteit hebben, de rustige ziekte niet het gevolg is van het toegediende medicijn, maar het gevolg is van het natuurlijk beloop van de RA (waarbij flares en rustige periodes elkaar afwisselen). Mogelijk zijn dit patiënten die hun medicijn zouden kunnen stoppen.
De hypothesen die worden getest zijn dan ook: 1) Patiënten met een hoge TNFi spiegel kunnen afbouwen en 2) Patiënten met geen meetbare TNFi spiegel kunnen stoppen.
Er wordt in dit onderzoek echter geen voorspellende waarde gevonden van bloedspiegels of antistoffen voor succesvol afbouwen of stoppen van TNFi in RA patiënten. Een uitzondering is dat een lagere etanerceptspiegel voorspellend is voor succesvol afbouwen. Deze bevinding past echter niet bij de hierboven beschreven hypothese waarin juist wordt gesteld dat patiënten met een hogere spiegel zouden kunnen afbouwen. In een extra analyse blijkt dat een hogere adalimumabspiegel geprikt vlak voor de volgende injectie (dalspiegel) voorspellend is voor succesvol afbouwen. Dit is wel in lijn met bovenstaande hypothese, maar omdat de bevinding tegengesteld is aan de bevinding bij etanercept, zou het een toevalsbevinding kunnen zijn. Daarom concluderen we dat we niet hebben kunnen aantonen dat medicatiespiegels en antistoffen voorspellend zijn voor succesvol afbouwen of stoppen.

Hoofdstuk 6: Algemene discussie

In het laatste hoofdstuk wordt een overzicht gegeven van de bevindingen van de verschillende onderzoeken in dit proefschrift en worden deze bevindingen bediscussieerd in de context van andere vergelijkbare onderzoeken. Verder wordt beschreven wat het belang van deze bevindingen is voor de dagelijkse praktijk en worden suggesties gedaan voor toekomstig onderzoek om de kennis uit dit proefschrift verder aan te vullen.

De belangrijkste conclusies uit dit proefschrift zijn:

- Ziekteactiviteit gestuurd afbouwen en stoppen van adalimumab, etanercept, abatacept en tocilizumab lijkt ook op de lange termijn haalbaar en veilig in RA patiënten (**hoofdstuk 2.1, hoofdstuk 4**).
- Afbouwen van TNFi in RA patiënten is kosteneffectief; ook als wordt afgebouwd buiten een studie protocol (**hoofdstuk 2.2**).
- Afbouwen van TNFi in RA patiënten vereist nauwgezette controle en follow-up om ziekteactiviteit zo laag mogelijk te houden en radiologische gewrichtsschade te voorkomen (**hoofdstuk 3**).
- Protocoladherentie bij reumatologen voor het afbouwen van bDMARDs in RA patiënten in de dagelijkse praktijk is suboptimaal (**hoofdstuk 4**).
- De multi-biomarker score en TNFi bloedspiegels en anti-TNFi antilichamen zijn niet voorspellend voor succesvol afbouwen of stoppen van TNFi in RA patiënten (**hoofdstuk 5.1, hoofdstuk 5.2**).

List of publications

Chapters in this thesis

1. Bouman CAM, van der Maas A, van Herwaarden N, Sasso EH, van den Hoogen FHJ, den Broeder AA. A multi-biomarker score measuring disease activity in rheumatoid arthritis patients tapering adalimumab or etanercept: predictive value for clinical and radiographic outcomes. Rheumatology (Oxford). 2017;56(6):973-980.
2. Bouman CAM, van Herwaarden N, van den Hoogen FHJ, Fransen J, van Vollenhoven RF, Bijlsma JW, van der Maas A, den Broeder AA. Long-term outcomes after disease-activity-guided dose reduction of TNF inhibition in rheumatoid arthritis: 3-year data of the DRESS study – a randomised controlled pragmatic non-inferiority strategy trial. Annals of Rheumatic Diseases. 2017;76(10):1716-1722
3. Bouman CAM, den Broeder AA, van der Maas A, van den Hoogen FHJ, Landewé RB, van Herwaarden N. What causes a small increase in radiographic progression in rheumatoid arthritis patients tapering TNF inhibitors? Rheumatic and Musculoskeletal Diseases Open. 2017;3(1):e000327.
4. Bouman CAM, van Herwaarden N, van den Hoogen FHJ, van der Maas A, van den Bemt BJF, den Broeder AA. Prediction of successful dose reduction or discontinuation of adalimumab, etanercept or infliximab in rheumatoid arthritis patients using serum drug levels and antidrug antibody measurement. Expert Opinion on Drug Metabolism and Toxicology. 2017;13(6):597-604.

Conference abstracts

1. Prediction of successful dose reduction or discontinuation of adalimumab or etanercept using serum drug levels and anti-drug antibody measurement. Conferences: NVR Najaarsdagen Arnhem 2014 (poster); ACR Boston 2014 (poster); NVZA/NVPF ziekenhuisfarmaciedagen 2014 (best abstract, poster).
2. Predictive Value of a Multi-Biomarker Disease Activity Score for Successful Tapering of TNF Inhibitors in Rheumatoid Arthritis: Results of the DRESS Study. Conferences: EULAR Rome 2015 (abstract publication); NVR Najaarsdagen Arnhem 2015 (poster).
3. Associations of a Multi-Biomarker Disease Activity Score with Clinical and Radiographic Parameters in Rheumatoid Arthritis. Conferences: EULAR Rome 2015 (abstract publication); NVR Najaarsdagen Arnhem 2015 (poster).
4. The Multi-Biomarker Disease Activity Score in a TNF Inhibitor Tapering Study in Rheumatoid Arthritis Patients: Predictive Value for Successful Tapering, Flaring and Radiographic Progression. Conference: ACR San Francisco 2015 (poster).
5. Radiographic progression in rheumatoid arthritis patients tapering TNF inhibitors is primarily driven by mean disease activity over time, not so much by flaring or lower TNF inhibitor exposition. Conferences: ACR San Francisco 2015 (oral presentation); EULAR London 2016 (oral presentation).
6. Study ON Abatacept and Tocilizumab Attenuation (SONATA) in Rheumatoid Arthritis Patients: a Retrospective, Explorative Cohort Study. Conferences: EULAR Rome 2016 (abstract publication); NVR Najaarsdagen Arnhem 2016 (oral presentation).
7. Long-term effects of disease activity guided tapering of TNF inhibition in rheumatoid arthritis: 3 year extension study of a randomised controlled pragmatic non inferiority strategy study. Conferences: NVR Najaarsdagen Arnhem 2016 (oral presentation); ACR Washington 2016 (oral presentation).

Publications outside of this thesis

1. Clinical audit in gynecological cancer surgery: Development of a risk scoring system to predict adverse events. Kondalsamy-Chennakesavan S, Bouman C, De Jong S, Sanday K, Nicklin J, Land R, Obermair A. International Journal of Gynecologic Oncology. 2009;115(3):329-33.
2. Hospital costs associated with adverse events in gynecologic oncology. Kondalsamy-Chennakesavan S, Gordon L, Sanday K, Bouman C, De Jong S, Nicklin J, Land R, Obermair A. International Journal of Gynecologic Oncology. 2011;121(1):70-5
3. Adalimumab and etanercept serum (anti) drug levels are not predictive for successful dose reduction or discontinuation in rheumatoid arthritis. Van Herwaarden N, Bouman CAM, Van der Maas A, Van Vollenhoven RF, Bijlsma JW, Van den Hoogen FHJ, Den Broeder AA, Van den Bemt BJ. Annals of rheumatic diseases 2015;74(12):2260-1.
4. Een bijzondere reumatologische aandoening met dermatologische verschijnselen: multicentrische reticulohistiocytose - een case report. Bouman C, Romijn D, Jeurissen M, Pasch MC, Blokx WAM. Dubbelpublicatie in: Nederlands Tijdschrift voor Reumatologie, 2015-03 en Nederlands Tijdschrift voor Dermatologie, 2016-03.
5. Letter in response to the article of Chen et al: 'Drug trough levels predict therapeutic responses to dose reduction of adalimumab for rheumatoid arthritis patients during 24 weeks of follow-up'. Bouman CAM, Den Broeder A. E-letter in: Rheumatology, February 15, 2016;(http://rheumatology.oxfordjournals.org/content/55/1/143/reply#rheumatology_el_218)

Curriculum vitae

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Chantal Bouman werd op 5 oktober 1987 geboren te Velp. In 2005 behaalde ze haar gymnasium diploma aan het Sint Ludgercollege in Doetinchem. In hetzelfde jaar startte ze met de opleiding geneeskunde aan de Radboud Universiteit in Nijmegen. Tijdens haar studie liep ze stage op de afdeling chirurgie in het Radboudumc. Aansluitend deed ze een wetenschappelijke stage op het gebied van gynaecologische oncologie in het Royal Brisbane and Women's Hospital in Brisbane, Australië. Aan het eind van haar studie volbracht ze haar seniorcoschap chirurgie in het Dr. Horacio E. Oduber Hospitaal te Aruba. In november 2011 behaalde ze haar artsendiploma en begon ze haar eerste arts-assistentschap op de afdeling reumatologie in de Sint Maartenskliniek, onder leiding van Dr. Maurice Jeurissen, Dr. Henk Martens en Dr. Marcel Franssen. Daar ontstond de mogelijkheid van het doen van wetenschappelijk onderzoek, hetgeen uitmondde in een promotietraject. Ze werd hierin begeleid door Dr. Alfons den Broeder, Dr. Aatke van der Maas en Prof. dr. Frank van den Hoogen. Het huidige proefschrift is daarvan het resultaat.

Per oktober 2016 is ze begonnen met haar vooropleiding interne geneeskunde in het Rijnstate Ziekenhuis te Arnhem (opleider Dr. Louis Reichert), in het kader van de opleiding tot reumatoloog (opleider Dr. Annelies van Ede). Naast haar opleiding is ze sinds 2011 algemeen bestuurslid en secretaris bij KNMG District Groot Gelre. In haar vrije tijd loopt ze graag hard en speelt ze dwarsfluit. Chantal woont samen met Itgen Hansen.

Dankwoord

Dankwoord

En dan is het tijd voor het leukste staaltje schrijfwerk van dit promotietraject: het dankwoord. Als de woorden van dit laatste hoofdstuk op papier staan, kan het boek dicht. Alhoewel het heel fijn is dat de combinatie eindsprint-promotietraject en startsprint-vooropleiding-interne-geneeskunde van beperkte duur is, kan ik me eigenlijk nog niet goed voorstellen dat het er bijna op zit. Want promoveren is een soort achtbaan waar je vol goede moed instapt, je na een serie onverwachte wendingen toch een beetje (veel) begint te twijfelen of het allemaal nou zo'n goed idee was en als de vaart er dan lekker in zit, blijkt het tochtje ineens voorbij te zijn. Maar stiekem had ik veel van die verschillende hoogte-, en dieptepunten niet willen missen.
Dat een promotie zoveel verschillende kanten heeft, komt uiteraard doordat er heel veel verschillende mensen bij betrokken zijn. Het schilderij op de kaft van mijn proefschrift sluit daarop aan. Ik ontdekte dit schilderij bij toeval in een obscure tweedehandswinkel in Berlijn en hoe vaker ik ernaar keek, hoe meer verbindingen ik zag met mijn promotietraject. Zoals de personen in het schilderij op de kaft van dit proefschrift laten zien, is er soms veel variatie in hoe verschillende personen iets ervaren, zoals het beleven van een mooi klassiek concert. En dit kan niet alleen tussen personen variëren (inter-observer variabiliteit), maar ook binnen het individu (intra-observer variabiliteit). Het had daarmee een directe connectie met dit proefschrift: inter- en intra-observer variabiliteit keren meerdere keren terug in de methodologie en resultaten van een aantal onderzoeken. Uiteraard is er ook een directe verbinding met het overkoepelende thema van mijn proefschrift: het afbouwen van medicijnen waarbij voor verschillende patiënten verschillende doses nodig blijken zijn. Tot slot heb ik zelf de afgelopen jaren veel intra-observer variabiliteit ervaren doordat ik heel veel verschillende kanten van het promoveren heb gezien met verschillende soorten onderzoek, verschillende begeleiders en diverse collega's. Mijn dank gaat uit naar iedereen die heeft bijgedragen aan de totstandkoming van dit proefschrift. Een aantal mensen wil ik in het bijzonder noemen.

Allereerst **alle patiënten** die hebben deelgenomen aan de verschillende onderzoeken. Zonder jullie vertrouwen was dit alles niet gelukt. Ik vind het heel fijn dat we met de meeste uitkomsten van de onderzoeken uit dit proefschrift en vorige onderzoeken een directe vertaalslag maakten naar de praktijk.

Natuurlijk staat of valt een promotie met de begeleiding. In mijn geval een begeleider met regelmatig 'een leuk nieuw idee' en een bovenmatig optimistische insteek met betrekking tot planning en praktische mogelijkheden. Daarmee mag ik van geluk spreken, aangezien mijn promotietraject totaal anders liep dan verwacht. **Dr. A.A. den Broeder**, Alfons, je enthousiasme enorm aanstekelijk en je weet de meest technische wetenschappelijke terminologie met humoristische voorbeelden begrijpelijk te maken. Ook probeer je daadwerkelijk een promotietraject te smeden rondom iemands kwaliteiten. Dat kan alleen doordat je de personen die je begeleid echt probeert te leren kennen, zowel op werkvlak als daarbuiten. Zo hadden wij hier en daar een (bepruikte) muzikale samenwerking. En beter nog: wie kan er nou zeggen dat zijn sollicitatiegesprek werd beklonken met een viool/dwarsfluit duet!
Hoewel een leuk idee prima is om mee te beginnen, werd al snel een tweede copromotor ingeschakeld. **Dr. A. van der Maas**, Aatke, gelukkig durfde je het na die ene kennismakingsborrel wel aan. Ik heb veel geleerd van je strakke wekelijkse begeleiding, realistische planning en opbouwende kritiek. Daarnaast heb je me de basics van Stata geleerd en kan ik er nog steeds van genieten om met woeste programmeertaal en lange syntaxen prachtige output

tevoorschijn te toveren. Maar bovenal heb ik altijd het idee gehad dat ik bij je binnen kon wandelen voor zowel promotie-, als privé aangelegenheden en dat waardeer ik zeer.
Tot slot werd daar een geweldige promotor aan toegevoegd. **Prof. F.H.J. van den Hoogen**, Frank, je bent een ontzettend prettige en toegankelijke mentor, met name door je relativerende opmerkingen, bijvoorbeeld toen de spanning voorafgaand aan presentaties in reusachtige congreshallen hoog opliep. Ook waren jouw positieve mails een enorme steun in de rug, bijvoorbeeld bij een wel zeer vasthoudende medeauteur die van geen ophouden wist. Daarnaast probeer ik de instructie 'keep on smiling' nog dagelijks toe te passen.

Voor mijn keuze tot het leukste vakgebied binnen de geneeskunde ben ik dank verschuldigd aan de begeleiders tijdens mijn eerste baan op de reuma afdeling in de SMK: **Henk Martens, Marcel Franssen** en **Maurice Jeurissen**. Daar heb ik kennis gemaakt met: 1. veel markante patiënten, 2. gedegen dieetgewoontes zoals strakke lunch routines en warme melk bij grote visites en 3. het belang van heel veel humor tijdens het werk. Ook al vond ik zo'n eerste baan best spannend, ik heb het ervaren als een warm bad. Daarbij zijn jullie alle drie op eigen wijze enorm inspirerend, wat wordt onderstreept door de inmiddels lange serie ANIOS (waaronder ondergetekende) die binnen de kortste keren voor de opleiding reumatologie kozen.
Alle reumatologen en PA's in SMK Nijmegen dank ik voor de ontzettend fijne en leerzame tijd: **Alfons, Karen, Henk, Hans, Regina, Susan, Aatke, Marcel Flendrie, Joost van Zadelhoff, Agnes, Hatice, Annemiek, Maartje, Frank, Elien, Vincent, Esther, Marcel Franssen, Maurice, Joost Huijs**: jullie zijn een prachtig team. Ik heb van ieder van jullie net weer andere dingen geleerd. Ik bewonder de vaardigheid om uiterst efficiënt te werken en de drive om altijd te willen blijven verbeteren, maar nooit zonder heel veel humor en oog voor de patiënt en elkaar. Ik had me geen betere start van mijn loopbaan kunnen voorstellen.
Alle AIOS reumatologie van het Radboudumc: wat zijn jullie een gezellige club! Dank voor de fijne samenwerking in de SMK en de gezelligheid op congressen, etentjes en speeltuinmiddagen.
Dr. A.E. van Ede, Annelies, dank dat je voor ons de drempel om binnen te lopen altijd weet te reduceren tot nul. We hebben maar geluk met zo'n opleider.
Dank ook aan de **reumatologen en verpleegkundig specialisten in SMK Woerden** voor deelname aan de DRESS studie en de MBDA studie.
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Verder kwam er een aantal kamergenoten voorbij. **Nienke**, we hebben heel wat kilometers samen afgelegd, van het veelvuldig aantal keren op en neer door de gang voor het halen van kopjes thee ter pre-, per- en posthydratie, tot pauzewandelingen door het bos rondom de SMK en later zelfs meerdere Nijmeegse vierdaagses. En ook al hebben we het mysterie van 'de vissende man' niet kunnen oplossen, die meters waren essentiële klets-tijd.
Lieke, jij kwam halverwege mijn promotie p1.03 versterken en dat leidde niet alleen tot een aantal mooie gedeelde publicaties, gezellige gezamenlijke congresbezoekjes en gedeelde pre- presentatiestress, maar uiteindelijk zelfs tot een gedeelde promotiedag en –feest! Wel zo gezellig dat we samen op lokatiejacht konden gaan en de organisatieklussen als een geoliede machine hebben weten te verdelen. We maken er wat moois van!
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Thea en **Aad**, vanaf het begin heb ik me ontzettend welkom gevoeld bij jullie. De vaste etentjes op vrijdagavond waren essentieel om ons na een vermoeiende werkweek weer van inspiratie (Thea), bijzondere uitspraken (Aad) en broodnodige vitamines voorzien. Het afgelopen jaar was wellicht wat al te avontuurlijk, maar daar zijn jullie je heldhaftig doorheen gekomen. Nu weer vol goede moed samen naar concerten, op kookcursus en die verbouwing nou echt eens afmaken. Het gaat allemaal lukken.

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